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NEWS 42 Jan 29 Simultaneous left and right truncation added to COMPENDEX,
 ENERGY, INSPEC
NEWS 43 Feb 13 CANCERLIT is no longer being updated
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NEWS 46 Feb 24 TEMA now available on STN
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=> s bone morphogenetic protein? or BMP
L1 13855 BONE MORPHOGENETIC PROTEIN? OR BMP

=> s bone morphogenetic protein?
L2 11378 BONE MORPHOGENETIC PROTEIN?

=> s11 and (knockout or transgen? or deficien? or disrupt? or delet?)
L3 1377 L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR
DISRUPT? OR DELET?)

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L4 1139 L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR
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=> s11 and (knockout or transgen? or deficien?)
L5 871 L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN?)

=> s11 and (knockout or transgen?)
L6 501 L1 AND (KNOCKOUT OR TRANSGEN?)

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L6 ANSWER 1 OF 501 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS

INC

AN 2003.118029 BIOSIS

DN PREV200300118029

TI Consequences of knocking out ***BMP*** signaling in the mouse.

AJ Zhao, Guang-Quan (1)

CS (1) Cecil H. and Ida Green Center for Reproductive Biology Sciences,
 University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd.,
 Dallas, TX, 75390-9051, USA guang.zhao@utsouthwestern.edu USA

SO Genesis: The Journal of Genetics and Development, (January 2003, 2003)

Vol

35, No. 1, pp 43-56. print.

ISSN 1526-954X.

DT Article

LA English

AB During the past two decades, a significant amount of data has been
 accumulated revealing the intriguing functions of ***bone***
 morphogenetic ***proteins*** (BMPs) in all aspects of
 embryonic development and organogenesis. Numerous genes encoding BMPs,
 BMP receptors, and their downstream signal transducers have been
 mutated in the mouse through targeted mutagenesis. This review focuses on
 what is known about the role of ***BMP*** signaling in gastrulation,
 mesoderm formation, left-right asymmetry, neural patterning, skeletal and
 limb development, organogenesis, and gametogenesis as revealed by
 BMP -signaling mutants.

L6 ANSWER 2 OF 501 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS

INC

AN 2003.87882 BIOSIS

DN PREV200300087882

TI ***BMP*** signaling is required for septation of the outflow tract of
 the mammalian heart

AJ Delot, Emmanuele C., Bahamonde, Matthew E., Zhao, Manxu, Lyons, Karen
M.

(1)

CS (1) Department of Orthopaedic Surgery, UCLA School of Medicine, Los
 Angeles, CA, 90095, USA klyons@mednet.ucla.edu USA

SO Development (Cambridge), (January 2003, 2003) Vol 130, No. 1, pp

209-220. print

ISSN 0950-1991

DT Article

LA English

AB ***Bone*** ***morphogenetic*** ***proteins*** (BMPs)
 constitute a family of appr20 growth factors involved in a tremendous
 variety of embryonic inductive processes. BMPs elicit dose-dependent
 effects on patterning during gastrulation and gradients of ***BMP***
 activity are thought to be established through regulation of the relative
 concentrations of ***BMP*** receptors, ligands and antagonists. We
 tested whether later developmental events also are sensitive to reduced
 levels of ***BMP*** signaling. We engineered a ***knockout***
 mouse that expresses a ***BMP*** type II receptor that lacks half of
 the ligand-binding domain. This altered receptor is expressed at levels

comparable with the wild-type allele, but has reduced signaling capability. Unlike Bmp2-null mice, mice homozygous for this hypomorphic receptor undergo normal gastrulation, providing genetic evidence of the dose-dependent effects of BMPs during mammalian development. Mutants, however, die at midgestation with cardiovascular and skeletal defects, demonstrating that the development of these tissues requires wild-type levels of ***BMP*** signaling. The most striking defects occur in the outflow tract of the heart, with absence of septation of the conotruncus below the valve level and interrupted aortic arch, a phenotype known in humans as persistent truncus arteriosus (type A4). In addition, semilunar valves do not form in mutants, while the atrioventricular valves appear unaffected. Abnormal septation of the heart and valve anomalies are the most frequent forms of congenital cardiac defects in humans, however, most mouse models display broad defects throughout cardiac tissues. The more restricted spectrum of cardiac anomalies in Bmp2DELTAE2 mutants makes this strain a key murine model to understand the embryonic defects of persistent truncus arteriosus and impaired semilunar valve formation in humans.

L6 ANSWER 3 OF 501 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC
 AN 2003 80130 BIOSIS
 DN PREV200300080130
 T: Atrioventricular valves and conduction defects following conditional deletion of ALK3, the type Ia receptor for ***bone*** ***morphogenetic*** ***proteins***, in cardiac myocytes of the atrioventricular canal.
 AU Gauvin, Vinciane (1); Liu, Jing (1); Mishina, Yuji, Hanks, Mark C.; Birch, John B.
 CS (1) UMDNJ-New Jersey Medical Sch, Newark, NJ, USA USA
 SO Circulation, (November 5 2002) Vol. 106, No. 19 Supplement, pp II-238. print.
 Meeting Info: Abstracts from Scientific Sessions Chicago, IL, USA November 17-20, 2002 American Heart Association
 ISSN 0009-7322
 DT Conference
 LA English

L5 ANSWER 4 OF 501 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC
 AN 2003 80091 BIOSIS
 DN PREV200300080091
 T: GATA and Smad transcription factors cooperatively interact to activate the Nkx2-5 gene
 AU Brown, Carl Oscar (1); Schwartz, Robert J. (1)
 CS (1) Baylor Coll of Medicine, Houston, TX, USA USA
 SO Circulation, (November 5 2002) Vol. 106, No. 19 Supplement, pp II-237. print.
 Meeting Info: Abstracts from Scientific Sessions Chicago, IL, USA November 17-20, 2002 American Heart Association
 ISSN 0009-7322
 DT Conference
 LA English

L6 ANSWER 5 OF 501 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC
 AN 2003 70216 BIOSIS
 DN PREV200300070216
 T: Interleukin-11 as a stimulatory factor for bone formation prevents bone loss with advancing age in mice
 AU Takeuchi, Yasuhiro (1); Watanabe, Sumiyo; Ishii, Genichiro; Takeda, Shu; Nakayama, Konosuke; Fukumoto, Seiji; Kaneta, Yasuyuki; Inoue, Daisuke; Matsumoto, Toshio; Horigaya, Kenichi; Fujita, Toshiro
 CS (1) Division of Endocrinology, Dept. of Medicine, University of Tokyo School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan; takeuchi-tky@umin.ac.jp Japan
 SO Journal of Biological Chemistry, (December 13 2002) Vol. 277, No. 50, pp. 49011-49018. print.
 ISSN: 0021-9258.

DT Article
 LA English
 AB Cytokines in interleukin (IL)-11 subfamily participate in the regulation of bone cell proliferation and differentiation. We report here positive effects of IL-11 on osteoblasts and bone formation. Overexpression of human IL-11 gene in ***transgenic*** mice resulted in the stimulation of bone formation to increase cortical thickness and strength of long bones, and in the prevention of cortical bone loss with advancing age. Bone resorption and osteoclastogenesis were not affected in IL-11 ***transgenic*** mice. In experiments in vitro, IL-11 stimulated transcription of the target gene for ***bone*** ***morphogenetic*** ***protein*** (***BMP***) via STAT3, leading to osteoblastic differentiation in the presence of ***BMP***, but inhibited adipogenesis in bone marrow stromal cells. These results indicate that IL-11 is a stimulatory factor for osteoblastogenesis and bone formation to conserve cortical bone, possibly by enhancing ***BMP*** actions in bone. IL-11 may be a new therapeutic target for senile osteoporosis.

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 L7 258 L1 (5a) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DELET?)

=> dup rem 17
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 L8 137 DUP REM L7 (121 DUPLICATES REMOVED)
 => s BMP-4
 L9 1625 BMP-4
 => s19 and (knockout or transgen? or deficien? or disrupt? or delet?)
 L10 174 L9 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DELET?)
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 L11 86 DUP REM L10 (88 DUPLICATES REMOVED)
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 L11 ANSWER 1 OF 86 CAPLUS COPYRIGHT 2003 ACS
 AN 2003 175965 CAPLUS
 TI Fabrication of homogeneously cross-linked, functional alginate microcapsules validated by NMR-, CLSM- and AFM-imaging
 AU Zimmermann, H.; Hilgartner, M.; Manz, B.; Feilen, P.; Brunnemann, F.; Leinfelder, U.; Weber, M.; Cramer, H.; Schneider, S.; Hendrich, C.; Volke, F.; Zimmermann, U.
 CS Arbeitsgruppe Tieftemperatur-Biophysik, Fraunhofer Institut für Biomedizinische Technik (IBMT), St. Ingbert, 66386, Germany
 SO Biomaterials (2003), 24(12), 2083-2096
 CODEN BIMADU, ISSN: 0142-9612
 PB Elsevier Science Ltd.
 DT Journal
 LA English
 AB Cross-linked alginate microcapsules of sufficient mech. strength can immunoisolate cells for the long-term treatment of hormone and other ***deficiency*** diseases in human beings. However, gelation of alginate by external Ba2+ (or other divalent cations) produces non-homogeneous crosslinking of the polymeric mannuronic (M) and guluronic (G) acid chains. The stability of such microcapsules is rather limited. Here, we show that homogeneous crosslinking can be achieved by injecting BaCl2 crystals into alginate droplets before they come into contact with external BaCl2. The high effectiveness of this crystal gun method is demonstrated by confocal laser scanning microscopy and by advanced NMR imaging. Both techniques gave clear-cut evidence that homogeneous cross-linkage throughout the microcapsule is only obtained with simultaneous internal and external gelation. At force microscopy showed a very smooth surface topog. for microcapsules made by the crystal gun method, provided that excess Ba2+ ions were removed immediately after gelation. In vitro expts. showed greatly suppressed swelling for crystal gun microcapsules. Even alginate extd. from *Lessonia nigrescens* (highly biocompatible) yielded microcapsules with long-term mech. stability not hitherto possible. Encapsulation of rat islets, human monoclonal antibodies secreting hybridoma cells and murine mesenchymal stem cells transfected with cDNA encoding for bone morphogenetic protein (***BMP*** - ***4***) revealed that injection of BaCl2 crystals has no adverse side effects on cell viability and function. However, the release of low-mol. wt. factors (such as insulin) may be delayed when using alginate concns. in the usual range.

L11 ANSWER 2 OF 86 EMBASE COPYRIGHT 2003 ELSEVIER SCI
 B V DUPLICATE 1
 AN 2003071240 EMBASE
 TI Involvement of bone morphogenetic protein 4 (***BMP*** - ***4***) in pituitary prolactinoma pathogenesis through a Smad/estrogen receptor crosstalk
 AU Paez-Pereira M.; Giacomini D.; Rejofa D.; Nagashima A.C.; Hopfner U.; Grubler Y.; Chervin A.; Goldberg V.; Goya R.; Hentges S.T.; Low M.J.; Holsboer F.; Stalla G.K.; Arzt E.
 CS E. Arzt, Departamento de Fisiología, Universidad de Buenos Aires, Ciudad Universitaria, C1428EA Buenos Aires, Germany eartz@ibmc.fcen.uba.ar
 SO Proceedings of the National Academy of Sciences of the United States of America, (4 Feb 2003) 100(3) 1034-1039
 Refs. 45
 ISSN: 0027-8424 CODEN: PNASA6
 CY United States
 DT Journal, Article
 FS 003 Endocrinology
 005 General Pathology and Pathological Anatomy
 LA English
 SL English
 AB Pituitary tumor development involves clonal expansion stimulated by hormones and growth factors/cytokines. Using mRNA differential display, we found that the bone morphogenetic protein (BMP) inhibitor noggin is down-regulated in prolactinomas from dopamine D2-receptor- ***deficient*** mice. ***BMP*** - ***4*** is overexpressed in prolactinomas taken from dopamine D2-receptor- ***deficient*** female mice, but expression of the highly homologous BMP-2 does not differ in normal pituitary tissue and prolactinomas. ***BMP*** - ***4*** is overexpressed in other prolactinoma models, including estradiol-induced rat prolactinomas and human prolactinomas, compared with normal tissue and other pituitary adenoma types (Western blot analysis of 48 tumors). ***BMP*** - ***4*** stimulates, and noggin blocks, cell proliferation and the expression of c-Myc in human prolactinomas, whereas ***BMP*** - ***4*** has no action in other human pituitary tumors. GH3 cells stably

transfected with a dominant negative of Smad4 (Smad4dn, a BMP signal cotransducer) or noggin have reduced tumorigenicity in nude mice. Tumor growth recovered in vivo when the Smad4dn expression was lost, proving that ***BMP*** - ***4*** /Smad4 are involved in tumor development in vivo. ***BMP*** - ***4*** and estrogen act through overlapping intracellular signaling mechanisms on GH3 cell proliferation and c-myc expression; they had additive effects at low concentrations but not at saturating doses, and their action was inhibited by blocking either pathway with the reciprocal antagonist (i.e., ***BMP*** - ***4*** with ICI 182780 or 17 beta-estradiol with Smad4dn). Furthermore, coimmunoprecipitation studies demonstrate that under ***BMP*** - ***4*** stimulation Smad4 and Smad1 physically interact with the estrogen receptor. This previously undescribed prolactinoma pathogenesis mechanism may participate in tumorigenicity in other cells where estrogens and the type beta transforming growth factor family have important roles.

L11 ANSWER 3 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC DUPLICATE

2
AN 2003 125434 BIOSIS
DN PREV200300125434

TI Sonic hedgehog cascade is required for penile postnatal morphogenesis, differentiation, and adult homeostasis
AU Podlasek, Carol A. (1), Zeiner, David J. (1), Jiang, Hong Bin (1), Tang, Yi (1), Houston, John (1), McKenna, Kevin E. (1), McVary, Kevin T (1)
CS (1) Department of Urology, Northwestern University, 303 E. Chicago Ave, Tarry Building 11-715, Chicago, IL, 60611, USA cap325@northwestern.edu USA

SO Biology of Reproduction, (February 2003, 2003) Vol. 68, No. 2, pp. 423-438. print.
ISSN 0006-3363.

DT Article
LA English

AB The penis is unique in that it undergoes morphogenesis and differentiation primarily in the postnatal period. For complex structures such as the penis to be made from undifferentiated precursor cells, proliferation, differentiation, and patterning are required. This process involves coordinated activity of multiple signals. Sonic hedgehog (Shh) forms part of a regulatory cascade that is essential for growth and morphogenesis of many tissues. It is hypothesized that the penis utilizes regulatory mechanisms similar to those of the limb and accessory sex organs to pattern penile postnatal morphogenesis and differentiation and that the Shh cascade is critical to this process. To test this hypothesis, Shh, ***BMP*** - ***4***, Ptc, and Hoxa-10 localization and function were examined in Sprague-Dawley rat penes by means of quantitative reverse transcriptase polymerase chain reaction, *in situ* hybridization, immunohistochemistry, and Western blotting. These genes were expressed in the penis during postnatal morphogenesis in a spatially and temporally restricted manner in adjacent layers of the corpora cavernosal sinusoids. The function of Shh and ***BMP*** - ***4*** is to establish and maintain corpora cavernosal sinusoids. The data suggest that Ptc and Hoxa-10 are also important in penile morphogenesis. The continuing function of Shh and targets of its signaling in maintaining penile homeostasis in the adult is significant because ***disruption*** of Shh signaling affects erectile function. This is the first report that demonstrates the significant role that Shh plays in establishing and maintaining penile homeostasis and how this relates to erectile function. These studies provide valuable insight that may be applied to improve treatment options for erectile dysfunction.

L11 ANSWER 4 OF 86 CAPLUS COPYRIGHT 2003 ACS

AN 2002 704574 CAPLUS
DN 137 228919

TI Immortalized periodontal ligament cell lines from ***transgenic*** rats carrying large T antigen gene of a temperature-sensitive mutant of SV40
IN Miki, Mirei; Kubota, Mamoru; Mitani, Hideo; Tatewaki, Masuo; Ueda, Shoji
PA Tohoku Techno Arch Co., Ltd., Japan
SO Jpn Kokai Tokkyo Koho, 28 pp
CODEN: JKXXAF

DT Patent
LA Japanese

FAN CNT 1

PATENT NO KIND DATE APPLICATION NO. DATE

PI JP 2002262862 A2 20020917 JP 2001-69249 20010312
PRAI JP 2001-69249 20010312
AB Described are ***transgenic*** rats obtained by introduction of a large T antigen gene of an SV40 temp. sensitive mutant tsA58 into rat omnipotent cells, and the established periodontal ligament (periodental membrane) cell lines prep'd from them. Cell lines are derived from rat periodontal ligament fibroblast, cementoblast, osteoclast, mesenchymal stem cell, Type I collagen, osteopontin, osteocalcin, bone morphogenetic protein 4 (***BMP*** - ***4***), bone sialoprotein (BSP), Core binding factor alpha 1 (Cbfa-1), glyceraldehyde 3-phosphate dehydrogenase (G3PDH), alk phosphatase (ALP), receptor activator of NF kappa beta Ligand (RANKL), or osteoprotegerin (OPG), may be used as cell surface marker for the cell lines. Gene expression for those proteins can be det'd by RT-PCR. Use of the cell lines for drug screening is claimed

L11 ANSWER 5 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2002 241813 BIOSIS

DN PREV200200241813

TI Retinoid signaling regulates primitive (yolk sac) hematopoiesis

AU Ghatpande, Satish; Ghatpande, Ashwin; Sher, Justin; Zile, Maija H.; Evans, Todd (1)

CS (1) Department of Developmental and Molecular Biology, Albert Einstein College of Medicine, 1300 Morris Park Ave, Chanin 501, Bronx, NY, 10461; tevans@aecom.yu.edu USA

SO Blood, (April 1, 2002) Vol. 99, No. 7, pp. 2379-2386.

http://www.bloodjournal.org/print

ISSN: 0006-4971

DT Article

LA English

AB It is known from nutritional studies that vitamin A is an important factor for normal hematopoiesis, though it has been difficult to define its precise role. The vitamin A- ***deficient*** (VAD) quail embryo provides an effective ligand " ***knockout*** " model for investigating the function of retinoids during development. The VAD embryo develops with a significant reduction in erythroid cells, which has not been noted previously. Activation of the primitive erythroid program and early expression of the erythroid marker GATA-1 occurs, though GATA-1 levels eventually decline, consistent with the erythropoietic and hemoglobin deficits. However, from its early stages, the GATA-2 gene fails to be expressed normally in VAD embryos. The bone morphogenetic protein (BMP)-signaling pathway regulates GATA-2, and BMP4 expression becomes reduced in the caudal embryonic region of VAD embryos. Adding BMP4 to cultured VAD-derived explants rescues the production of erythroid cells, whereas normal embryos cultured in the presence of the BMP antagonist noggin are defective in primitive hematopoiesis. We find that cell clusters of primitive blood islands undergo an inappropriate program of apoptosis in the VAD embryo, which can explain the deficit in differentiated primitive blood cells. We propose that vitamin A-derived retinoids are required for normal yolk sac hematopoiesis and that an embryonic retinoid-BMP-GATA-2 signaling pathway controls progenitor cell survival relevant to primitive hematopoiesis

L11 ANSWER 6 OF 86 CAPLUS COPYRIGHT 2003 ACS

AN 2002 469141 CAPLUS

DN 137 167335

TI Wild-type levels of the mouse Forkhead Box f1 gene are essential for lung repair

AU Kalnichenko, Vladimir V.; Zhou, Yan; Shin, Brian; Stoltz, Donna Beer; Watkins, Simon C.; Whitsett, Jeffrey A.; Costa, Robert H

CS Department of Molecular Genetics, College of Medicine, University of Illinois at Chicago, Chicago, IL, 60607-7170, USA

SO American Journal of Physiology (2002), 282(6, Pt. 1), L1253-L1265
CODEN: AJPHAP; ISSN: 0002-9513

PB American Physiological Society

DT Journal

LA English

AB The Forkhead Box (Fox) family of transcription factors plays important roles in regulating expression of genes involved in cellular proliferation and differentiation. In a previous study, we showed that newborn fox1(+/-) mice with diminished Fox1 levels exhibited abnormal formation of pulmonary alveoli and capillaries and died postnatally. Interestingly, surviving newborn fox1(+/-) mice exhibited increased pulmonary Fox1 levels and normal adult lung morphol., suggesting that wild-type Fox1 levels are required for lung development and function. The present study was conducted to det. whether adult fox1(+/-) mice were able to undergo lung repair similar to that obsd. in wild-type mice. We demonstrated that adult fox1(+/-) mice died from severe lung hemorrhage after butylated hydroxytoluene (BHT) lung injury and that this phenotype was assoc'd. with a 10-fold decrease in pulmonary Fox1 expression and increased alveolar endothelial cell apoptosis that ***disrupted*** capillary integrity. Furthermore, BHT-induced lung hemorrhage of adult fox1(+/-) mice was assoc'd. with a drastic redn. in expression of the Flik-1, bone morphogenetic protein-4, surfactant protein B, platelet endothelial cell adhesion mol., and vascular endothelial cadherin genes, whereas the expression of these genes was either transiently diminished or increased in wild-type lungs after BHT injury. Because these proteins are cnt. for lung morphogenesis and endothelial homeostasis, their decreased mRNA levels are likely contributing to BHT-induced lung hemorrhage in fox1(+/-) mice. Collectively, our data suggest that sustained expression of Fox1 is essential for normal lung repair and endothelial cell survival in response to pulmonary cell injury

RE CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD
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L11 ANSWER 7 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC DUPLICATE

3

AN 2002 418048 BIOSIS

DN PREV200200418048

TI Ex vivo gene therapy with stromal cells transduced with retroviral vector containing the BMP4 gene completely heals/critical size calvarial defect in rats

AU Gysin, R.; Wergedal, J. E.; Sheng, M. H.-C.; Kasukawa, Y.; Miyakoshi, N.; Chen, S.-T.; Peng, H.; Lau, K.-H. W.; Mohan, S.; Baylink, D. J. (1)

CS (1) Musculoskeletal Disease Center, Jerry L Pettis Memorial VA Medical Center, 11201 Benton Street, 151, Loma Linda, CA, 92357 USA

SO Gene Therapy, (August, 2002) Vol. 9, No. 15, pp. 991-999

http://www.naturej.com/gt/print

DT Article

LA English

AB In order to develop a successful gene therapy system for the healing of bone defects, we developed a murine leukemia virus (MLV)-based retroviral system expressing the human bone morphogenetic protein (***BMP*** - ***4*** - ***transgene*** with high transduction efficiency. The bone formation potential of BMP4 transduced cells was tested by embedding 2.5X106 transduced stromal cells in a gelatin matrix that was then placed in a critical size defect in calvariae of syngenic rats. Gelatin matrix without cells or with untransduced stromal cells were the two control groups. The defect area was completely filled with new bone in experimental rats after 4 weeks, while limited bone formation occurred in either control group. Bone mineral density (BMD) of the defect in the gene therapy group was 67.8+/-5.7 mg/cm2 (mean+/-s.d., n=4), which was 119+/-10% of the control BMD of bone surrounding the defect (57.2+/-1.5 mg/cm2). In contrast, BMD of rats implanted with untransduced stromal cells was five-fold lower (13.8+/-7.4 mg/cm2, P<0.001). Time course studies revealed that there was a linear increase in BMD between 2-4 weeks after inoculation of the critical size defect with 2.5X106 implanted BMP4 cells. In conclusion, the retroviral-based BMP4 gene therapy system that we have developed has the potential for regeneration of large skeletal defects.

L11 ANSWER 8 OF 86 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC DUPLICATE

4

AN 2003 27391 BIOSIS

DN PREV20030027391

TI Transcriptional regulation of Xbr-1a/Xvent-2 homeobox gene: Analysis of its promoter region

AU Lee, Hyun-Shik, Park, Mae-Ja, Lee, Sung-Young, Hwang, Yoo-Seok, Lee, Hyosang, Roh, Dong-Hyun, Kim, Jong-Il, Park, Jae-Bong, Lee, Jae-Yong, Kung, Hsiang-Fu, Kim, Jaebong (1)

CS (1) Department of Biochemistry, College of Medicine, Hallym University, Chuncheon, Kangwon-Do, 200-702, South Korea jbkim@hallym.ac.kr South Korea

SO Biochemical and Biophysical Research Communications, (November 15 2002) Vol. 298, No. 5, pp. 815-823 print ISSN 0006-291X

DT Article

LA English

AB Xvent homeobox proteins are induced by ***BMP*** - ***4*** signaling and have been known to mediate many ***BMP*** - ***4*** activities as key downstream transcriptional factors. In order to investigate the regulatory mode of Xvent transcription, we isolated genomic DNA of the Xbr-1a/Xvent-2 containing the promoter region responsive to ***BMP*** - ***4*** signaling. The cis-acting elements located within the Xbr-1a/Xvent-2 promoter and the regulation modes by ***BMP*** - ***4*** signaling were analyzed by serial ***deletion*** and site-directed mutagenesis experiments. The upstream -235 bp of the promoter retained the full transcriptional activity and ***BMP*** - ***4*** -response when compared with the longest promoter construct. Further analysis indicated that two separated 15 bp regions contained a strong positive element and ***BMP*** - ***4*** -response element. Site-directed mutagenesis of those regions suggests that those two regions cooperate for the promoter activity and ***BMP*** - ***4*** -response. Moreover, we found that the transcription factors, Oaz and PEBP2alphaA, were able to elicit additive effects with ***BMP*** - ***4*** signaling on Xbr-1a/Xvent-2 reporter activities. These results indicate that transcriptional regulation of the Xbr-1a/Xvent-2 gene occurs in a complex mode through the cooperation of various transcription factors.

L11 ANSWER 9 OF 86 CAPLUS COPYRIGHT 2003 ACS

AN 2002 715472 CAPLUS

DN 138 640

TI Msx2 and p21CIP1/WAF1 mediate the proapoptotic effects of bone morphogenetic protein-4 on ventricular zone progenitor cells

AU Israsena, Niran, Kessler, John A.

CS Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA

SO Journal of Neuroscience Research (2002), 69(6), 803-809 CODEN JNREDK, ISSN 0360-4012

PB Wiley-Liss, Inc.

DT Journal

LA English

AB Treatment of cultured ventricular zone (VZ) progenitor cells with bone morphogenetic protein-4 (BMP4) promoted cell death in a dose-dependent manner. VZ progenitor cells became progressively more resistant to the proapoptotic effects of BMP4 between E10 and E16, and, by E18 and thereafter, BMP4 treatment no longer led to progenitor cell death. BMP4 treatment of E13 progenitor cells promoted expression of msx2 and p21CIP1/WAF1 (p21) and inhibition of expression of either gene prevented BMP4-mediated apoptosis. Treatment of E18 cells with BMP4 failed to induce apoptosis but still induced expression of low levels of msx2 and p21. ***Knockout*** of both significantly reduced but did not prevent BMP4-mediated death of E13 murine progenitor cells. These observations indicate that msx2 and p21 mediate the proapoptotic effects of BMP4 on VZ progenitor cells and that each gene is necessary but insufficient to promote apoptosis.

RE CNT 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 10 OF 86 EMBASE COPYRIGHT 2003 ELSEVIER SCI

B V DUPLICATE 5

AN 2002409795 EMBASE

TI Generation of neuroendocrine chromaffin cells from sympathetic adrenal progenitors: Beyond the glucocorticoid hypothesis

AU Huber K, Combs S, Erensberger U, Kalcheim C, Unsicker K.

CS K. Unsicker, Department of Neuroanatomy, Inst for Anatomy and Cell Biology, University of Heidelberg, Im Neuenheimer Feld 307, D-69120 Heidelberg, Germany, klaus.unsicker@urz.uni-heidelberg.de

SO Annals of the New York Academy of Sciences, (5 Jun 2002) 971/- (554-559)

Refs 14

ISSN 0077-8923 CODEN ANYAA

CY United States

DT Journal/Conference Article

FS 003 Endocrinology

008 Neurology and Neurosurgery

LA English

SL English

AB The developmental diversification of neural crest-derived sympathetic adrenal (SA) progenitor cells into neuroendocrine adrenal chromaffin cells and sympathetic neurons has been thought to be largely understood. Based on two decades of *in vitro* studies with isolated SA progenitor and chromaffin cells, it was widely assumed that chromaffin cell development crucially depends on glucocorticoid hormones provided by adrenal cortical cells.

However, analysis of mice lacking the glucocorticoid receptor has revealed that the chromaffin cell phenotype develops largely normally in these mice, except for the induction of the adrenaline synthesizing enzyme phenylethylamine N-methyl transferase. In a search for novel candidate genes that might be involved in triggering the sympathetic neuron/chromaffin cell decision, we have studied putative contributions of transforming growth factor (TGF)-beta, ***BMP*** - ***4***, and the transcription factor MASH-1, molecules with distinct expressions in SA progenitor cells, in their migratory pathways and final destinations.

TGF-beta 2 and -beta 3 and ***BMP*** - ***4*** are highly expressed in the wall of the dorsal aorta and in the adrenal anlagen during and after immigration of SA progenitors but expressed at much lower levels in sympathetic ganglia. We found that neutralizing antibodies against all three TGF-beta isoforms applied to the chorionicallantoic membrane (CAM) of quail embryos interfere with proliferation of immigrated adrenal chromaffin cells but do not affect their specific neuroendocrine ultrastructural phenotype. Grafting of noggin-producing cells to the CAM, which scavenges BMPs, interferes with visceral arch and limb development but does not overtly affect the chromaffin phenotype. The transcription factor MASH-1 promotes early differentiation of SA progenitors. Mice ***deficient*** for MASH-1 lack sympathetic ganglia, whereas the adrenal medulla previously has been reported to be present. We show here that most adrenal medullary cells in MASH-1(-/-) mice identified by Phox2b immunoreactivity lack the catecholaminergic marker tyrosine hydroxylase. More surprisingly, most cells do not contain chromaffin granules and display a neuroblast-like ultrastructure and show strongly enhanced expression of c-RET comparable to that observed in sympathetic ganglia. Together, our data suggest that TGF-beta's and ***BMP*** - ***4*** do not seem to be essential for chromaffin cell differentiation. In contrast with previous reports, however, MASH-1 apparently plays a crucial role in chromaffin cell development.

> d his

FILE 'HOME' ENTERED AT 11.05.42 ON 13 MAR 2003

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11.06.21 ON 13 MAR 2003

L1 13855 S BONE MORPHOGENETIC PROTEIN? OR BMP

L2 11378 S BONE MORPHOGENETIC PROTEIN?

L3 1377 S L1 AND (*NOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DEL

L4 1139 S L1 AND (*NOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT?)

L5 871 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN?)

L6 501 S L1 AND (KNOCKOUT OR TRANSGEN?)

L7 258 S L1 (SA) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DE

L8 137 DUP REM L7 (121 DUPLICATES REMOVED)

L9 1625 S BMP-4

L10 174 S L9 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DE

L11 86 DUP REM L10 (88 DUPLICATES REMOVED)

> s i8 or i11

L12 203 L8 OR L11

> d bib abs l12 1:10

L12 ANSWER 1 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2003 125434 BIOSIS

DN PREV200300125434

TI Sonic hedgehog cascade is required for penile postnatal morphogenesis, differentiation, and adult homeostasis

AU Podlasek, Carol A (1), Zelner, David J, Jiang, Hong Bin, Tang, Yi,

Houston, John, McKenna, Kevin E, McVary, Kevin T

CS (1) Department of Urology, Northwestern University, 303 E Chicago Ave.

Terry Building 11-715, Chicago, IL, 60611, USA cap325@northwestern.edu
USA
SO Biology of Reproduction, (February 2003, 2003) Vol 68, No 2, pp 423-438 print
ISSN 0006-3363

DT Article
LA English
AB The penis is unique in that it undergoes morphogenesis and differentiation primarily in the postnatal period. For complex structures such as the penis to be made from undifferentiated precursor cells, proliferation, differentiation, and patterning are required. This process involves coordinated activity of multiple signals. Sonic hedgehog (Shh) forms part of a regulatory cascade that is essential for growth and morphogenesis of many tissues. It is hypothesized that the penis utilizes regulatory mechanisms similar to those of the limb and accessory sex organs to pattern penile postnatal morphogenesis and differentiation and that the Shh cascade is critical to this process. To test this hypothesis, Shh, ***BMP*** - ***4***, Ptc, and Hoxa-10 localization and function were examined in Sprague-Dawley rat penes by means of quantitative reverse transcription polymerase chain reaction, *in situ* hybridization, immunohistochemistry, and Western blotting. These genes were expressed in the penis during postnatal morphogenesis in a spatially and temporally restricted manner in adjacent layers of the corpora cavernosal sinusoids. The function of Shh and ***BMP*** - ***4*** is to establish and maintain corpora cavernosal sinusoids. The data suggest that Ptc and Hoxa-10 are also important in penile morphogenesis. The continuing function of Shh and targets of its signaling in maintaining penile homeostasis in the adult is significant because ***disruption*** of Shh signaling affects erectile function. This is the first report that demonstrates the significant role that Shh plays in establishing and maintaining penile homeostasis and how this relates to erectile function. These studies provide valuable insight that may be applied to improve treatment options for erectile dysfunction.

L12 ANSWER 2 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2003 87882 BIOSIS

DN PREV200300087882

TI BMP signaling is required for septation of the outflow tract of the mammalian heart.

AU Delot, Emmanuelle C ; Bahamonde, Matthew E ; Zhao, Manxu, Lyons, Karen M
(1)

CS (1) Department of Orthopaedic Surgery, UCLA School of Medicine, Los Angeles, CA, 90095, USA; klyons@mednet.ucla.edu USA

SO Development (Cambridge), (January 2003, 2003) Vol. 130, No. 1, pp 209-220 print
ISSN 0950-1991.

DT Article

LA English

AB Bone morphogenetic proteins (BMPs) constitute a family of approx 20 growth factors involved in a tremendous variety of embryonic inductive processes. BMPs elicit dose-dependent effects on patterning during gastrulation and gradients of BMP activity are thought to be established through regulation of the relative concentrations of BMP receptors, ligands and antagonists. We tested whether later developmental events also are sensitive to reduced levels of ***BMP*** signaling. We engineered a ***knockout*** mouse that expresses a ***BMP*** type II receptor that lacks half of the ligand-binding domain. This altered receptor is expressed at levels comparable with the wild-type allele, but has reduced signaling capability. Unlike Bmp2-null mice, mice homozygous for this hypomorphic receptor undergo normal gastrulation, providing genetic evidence of the dose-dependent effects of BMPs during mammalian development. Mutants, however, die at midgestation with cardiovascular and skeletal defects, demonstrating that the development of these tissues requires wild-type levels of BMP signaling. The most striking defects occur in the outflow tract of the heart, with absence of septation of the conotruncus below the valve level and interrupted aortic arch, a phenotype known in humans as persistent truncus arteriosus (type A4). In addition, semilunar valves do not form in mutants, while the atrioventricular valves appear unaffected. Abnormal septation of the heart and valve anomalies are the most frequent forms of congenital cardiac defects in humans; however, most mouse models display broad defects throughout cardiac tissues. The more restricted spectrum of cardiac anomalies in Bmp2DELTAE2 mutants makes this a key murine model to understand the embryonic defects of persistent truncus arteriosus and impaired semilunar valve formation in humans.

L12 ANSWER 3 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2003 64210 BIOSIS

DN PREV200300064210

TI Estrogens activate bone morphogenetic protein-2 gene transcription in mouse mesenchymal stem cells

AU Zhou, Shuanhu, Turgeman, Gadi, Harris, Stephen E ; Leitman, Dale C, Kommineni, Barry S ; Bodine, Peter V N ; Gazit, Dan (1)

CS (1) Molecular Pathology Laboratory, Hebrew University-Hadassah Medical and

Gene Therapy Center, P O Box 12272, Jerusalem, 91120, Israel
dgaz@cc.huji.ac.il Israel

SO Molecular Endocrinology, (January 2003, 2003) Vol. 17, No. 1, pp 56-66 print
ISSN 0888-8809

DT Article

LA English

AB Estrogens exert their physiological effects on target tissues by interacting with the estrogen receptors, ERalpha and ERbeta. Estrogen replacement is one of the most common and effective strategies used to prevent osteoporosis in postmenopausal women. Whereas it was thought that estrogens work exclusively by inhibiting bone resorption, our previous results show that 17beta-estradiol (E2) increases mouse bone morphogenetic protein (BMP)-2 mRNA, suggesting that estrogens may also enhance bone formation. In this study, we used quantitative real-time RT-PCR analysis to demonstrate that estrogens increase BMP-2 mRNA in mouse mesenchymal stem cells. The selective ER modulators, tamoxifen, raloxifene, and ICI-182,780 (ICI), failed to enhance BMP-2 mRNA, whereas ICI inhibited E2 stimulation of expression. To investigate if estrogens increase BMP-2 expression by transcriptional mechanisms and if the response is mediated by ERalpha and/or ERbeta, we studied the effects of estrogens on BMP-2 promoter activity in transient transfected C3H10T1/2 cells. E2 produced a dose-dependent induction of the mouse -2712 BMP-2 promoter activity in cells cotransfected with ERalpha and ERbeta. At a dose of 10 nM E2, ERalpha induced mouse BMP-2 promoter activity 9-fold, whereas a 3-fold increase was observed in cells cotransfected with ERbeta. Tamoxifen and raloxifene were weak activators of the mouse BMP-2 promoter via ERalpha, but not via ERbeta. ICI blocked the activation of BMP-2 promoter activity by E2 acting via both ERalpha and ERbeta, indicating that mouse BMP-2 promoter activation is ER dependent. In contrast to E2 and selective ER modulators, the phytoestrogen, genistein was more effective at activating the mouse BMP-2 promoter with ERbeta, compared with ERalpha. Using a ***deletion*** series of the ***BMP*** -2 promoter, we determined that AP-1 or Sp1 sites are not required for E2 activation. A mutation in a sequence at -415 to -402 (5'-GGGCCActCT-GACCC-3') that resembles the classical estrogen-responsive element abolished the activation of the BMP-2 promoter in response to E2. Our studies demonstrate that E2 activation of mouse BMP-2 gene transcription requires ERalpha or ERbeta acting via a variant estrogen-responsive element binding site in the promoter, with ERalpha being the more efficacious regulator. Estrogenic compounds may enhance bone formation by increasing the transcription of the BMP-2 gene.

L12 ANSWER 4 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2003 43864 BIOSIS

DN PREV200300043864

TI Phenotypic effects of knockout of oocyte-specific genes

AU Varani, S (1), Matzuk, M M

CS (1) Department of Pathobiology, Baylor College of Medicine, One Baylor Plaza, Houston, TX, 77030, USA; svarani@bcm.edu, Mmatzuk@bcm.edu USA

SO Eppig, J [Editor], Hegele-Hartung, Ch. [Editor], Lessl, M [Editor]

Ernst Schering Research Foundation Workshop, (2002) Vol. 41, pp 63-79.

Ernst Schering Research Foundation Workshop: The future of the oocyte

Basic and clinical aspects, print

Publisher: Springer-Verlag New York Inc. 175 Fifth Avenue, New York, NY, 10010-7858, USA

Meeting Info: Ernst Schering Research Foundation Workshop 41 on The Future of the Oocyte: Basic and Clinical Aspects Berlin, Germany January 30-February 01, 2002 Ernst Schering Research Foundation

ISSN: 0947-6075. ISBN: 3-540-43747-9 (cloth)

DT Conference

LA English

L12 ANSWER 5 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2003 27391 BIOSIS

DN PREV200300027391

TI Transcriptional regulation of Xbr-1a/Xvent-2 homeobox gene: Analysis of its promoter region

AU Lee, Hyun-Shik, Park, Mae Ja, Lee, Sung-Young, Hwang, Yoo-Seok, Lee, Hyosang, Roh, Dong-Hyun, Kim, Jong-Il, Park, Jae-Bong, Lee, Jae-Yong, Kung, Hsiang-Fu, Kim, Jaebong (1)

CS (1) Department of Biochemistry, College of Medicine, Hallym University, Chuncheon, Gangwon-Do, 200-702, South Korea; jkjkim@hallym.ac.kr South Korea

SO Biochemical and Biophysical Research Communications, (November 15 2002) Vol. 298, No. 5, pp 815-823 print
ISSN: 0006-291X

DT Article

LA English

AB Xvent homeobox proteins are induced by ***BMP*** - ***4*** signaling and have been known to mediate many ***BMP*** - ***4*** activities as key downstream transcriptional factors. In order to investigate the regulatory mode of Xvent transcription, we isolated genomic DNA of the Xbr-1a/Xvent-2 containing the promoter region responsive to ***BMP*** - ***4*** signaling. The cis-acting elements located within the Xbr-1a/Xvent-2 promoter and the regulation modes by ***BMP*** - ***4*** signaling were analyzed by serial ***deletion*** and site-directed mutagenesis experiments. The upstream -235 bp of the promoter retained the full transcriptional activity and ***BMP*** - ***4*** -response when compared with the longest promoter construct. Further analysis indicated that two separated 15 bp regions contained a strong positive element and ***BMP*** - ***4*** -response element. Site-directed mutagenesis of those regions suggests that those two regions cooperate for the promoter activity and ***BMP*** - ***4*** -response. Moreover, we found that the transcription factors, Oaz and

PEPB2alphaA, were able to elicit additive effects with ***BMP*** - ***4*** signaling on Xbr-1a/Xvent-2 reporter activities. These results indicate that transcriptional regulation of the Xbr-1a/Xvent-2 gene occurs in a complex mode through the cooperation of various transcription factors.

L12 ANSWER 6 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2002 623445 BIOSIS

DN PREV200200623445

TI Noggin's required for correct guidance of dorsal root ganglion axons.

AU Dionne, Marc S., Brunet, Lisa J., Eimon, Peter M., Harland, Richard M. (1)

CS (1) Division of Genetics and Development, Department of Molecular and Cell Biology, University of California, Berkeley, CA, 94720-3202

harland@socrates berkeley.edu USA

SO Developmental Biology, (November 15, 2002) Vol. 251, No. 2, pp. 283-293

<http://www.academicpress.com/db> print

ISSN 0012-1606

DT Article

LA English

AB Members of the bone morphogenetic protein family of secreted protein signals have been implicated as axon guidance cues for specific neurons in *Caenorhabditis elegans* and in mammals. We have examined axonal pathfinding

in mice lacking the secreted bone morphogenetic protein antagonist Noggin. We have found defects in projection of several groups of neurons, including the initial ascending projections from the dorsal root ganglia, motor axons innervating the distal forelimb, and cranial nerve VII. The case of the dorsal root ganglion defect is especially interesting: initial projections from the dorsal root ganglion enter the dorsal root entry zone, as normal, but then project directly into the gray matter of the spinal cord, rather than turning rostrally and caudally. Explant experiments suggest that the defect lies within the spinal cord and not the dorsal root ganglion itself. However, exogenous bone morphogenetic proteins are unable to attract or repel these axons, and the spinal cord shows only very subtle alterations in dorsal-ventral pattern in Noggin mutants. We suggest that the defect in projection into the spinal cord is likely the result of ***bone*** ***morphogenetic*** ***proteins*** ***disrupting*** the transduction of some unidentified repulsive signal from the spinal cord gray matter

L12 ANSWER 7 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2002 614775 BIOSIS

DN PREV200200614775

TI Chordin and noggin promote organizing centers of forebrain development in the mouse

AU Anderson, Ryan M., Lawrence, Alison R., Stottmann, Rolf W., Bachiller, Daniel, Klingensmith, John (1)

CS (1) Department of Cell Biology, Duke University Medical Center, Durham, NC, 27710-3709 kling@cellbio.duke.edu USA

SO Development (Cambridge), (November, 2002) Vol. 129, No. 21, pp. 4975-4987

<http://dev.biologists.org/current.shtml> print

ISSN 0950-1991

DT Article

LA English

AB In this study we investigate the roles of the organizer factors chordin and noggin, which are dedicated antagonists of the bone morphogenetic proteins (BMPs), in formation of the mammalian head. The mouse chordin and noggin genes (*Chrd* and *Nog*) are expressed in the organizer (the node) and its mesendodermal derivatives, including the prechordal plate, an organizing center for rostral development. They are also expressed at lower levels in and around the anterior neural ridge, another rostral organizing center. To elucidate roles of *Chrd* and *Nog* that are masked by the severe phenotype and early lethality of the double null, we have characterized embryos of the genotype *Chrd*-/-, *Nog* +/- . These animals display partially penetrant neonatal lethality, with defects restricted to the head. The variable phenotypes include cyclopia, holoprosencephaly, and rostral truncations of the brain and craniofacial skeleton. In situ hybridization reveals a loss of SHH expression and signaling by the prechordal plate, and a decrease in FGF8 expression and signaling by the anterior neural ridge at the five-somite stage. Defective *Chrd*-/-, *Nog* +/- embryos exhibit reduced cell proliferation in the rostral neuroepithelium at 10 somites, followed by increased cell death 1 day later. Because these phenotypes result from reduced levels of BMP antagonists, we hypothesized that they are due to increased BMP activity. Ectopic application of BMP2 to wild-type cephalic explants results in decreased FGF8 and SHH expression in rostral tissue, suggesting that the decreased expression of FGF8 and SHH observed in vivo is due to ectopic BMP activity. Cephalic explants isolated from *Chrd*, *Nog* double mutant embryos show an increased sensitivity to ectopic BMP protein, further supporting the hypothesis that these mutants are ***deficient*** in ***BMP*** antagonism. These results indicate that the BMP antagonists chordin and noggin promote the inductive and trophic activities of rostral organizing centers in early development of the mammalian head

L12 ANSWER 8 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2002 602667 BIOSIS

DN PREV200200602667

TI The Fused toes (Ft) mouse mutation causes anteroposterior and dorsoventral polydactyly

AU Grotewold, Lars, Ruether, Ulrich (1)

CS (1) Institut fuer Entwicklungs- und Molekularbiologie der Tiere (EMT), Heinrich-Heine-Universitaet, 40225, Duesseldorf ruether@uni-duesseldorf.de

SO Developmental Biology, (November 1, 2002) Vol. 251, No. 1, pp. 129-141 <http://www.academicpress.com/db> print

ISSN: 0012-1606

DT Article

LA English

AB Mouse mutants have been proven to be a valuable system to analyze the molecular network governing vertebrate limb development. In the present study, we report on the molecular and morphological consequences of the Fused toes (Ft) mutation on limb morphogenesis in homozygous embryos. We show that Ft affects all three axes as the mutant limbs display severe distal truncations of skeletal elements as well as an anteroposterior and an unusual form of dorsoventral polydactyly. Ectopic activation of the Shh signalling cascade in the distal-most mesoderm together with malformations of the AER likely account for these alterations. Moreover, we provide evidence that a deregulated control of programmed cell death triggered by ***Bmp*** - ***4*** and Dkk-1 significantly contributes to the complex limb phenotype. In addition, our analysis reveals a specific requirement of the genes ***deleted*** by the Ft mutation in hindlimb morphogenesis

L12 ANSWER 9 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2002 565105 BIOSIS

DN PREV200200565105

TI BMP signaling is required for development of the ciliary body

AU Zhao, Shulei (1); Chen, Qin, Hung, Fang-Cheng, Overbeek, Paul A (1) Lexicon Genetics, 8800 Technology Forest Place, The Woodlands, TX, 77381 szhao@lexgen.com USA

SO Development (Cambridge), (October, 2002) Vol. 129, No. 19, pp. 4435-4442 <http://dev.biologists.org/current.shtml> print

ISSN: 0950-1991

DT Article

LA English

AB The ciliary body in the eye secretes aqueous humor and glycoproteins of the vitreous body and maintains the intraocular pressure. The ciliary muscle controls the shape of the lens through the ciliary zonules to focus the image onto the retina. During embryonic development, the ciliary epithelium is derived from the optic vesicle, but the molecular signals that control morphogenesis of the ciliary body are unknown. We report that lens-specific expression of a ***transgenic*** protein, Noggin, can block ***BMP*** signaling in the mouse eye and result in failure in formation of the ciliary processes. Co-expression of transgenic BMP7 restores normal development of the ciliary epithelium. Ectopic expression of Noggin also promotes differentiation of retinal ganglion cells. These results indicate that BMP signaling is required for development of the ciliary body and may also play a role in regulation of neuronal differentiation in the developing eye

L12 ANSWER 10 OF 203 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2002 564544 BIOSIS

DN PREV200200564544

TI Stem cell differentiation requires a paracrine pathway in the heart

AU Behfar, Atta, Zingman, Leonid V., Hodgson, Denice M., Rauzier, Jean-Michel, Kane, Garvan C., Terzic, Andre, Puceat, Michel (1)

CS (1) CRBM, CNRS UPR1086, 1919, Route de Mende, 34293, Montpellier puceat@crbm.cnrs-mop.fr France

SO FASEB Journal, (October, 2002) Vol. 16, No. 12, pp. 1558-1566 <http://www.faseb.org/> print

ISSN: 0892-6638

DT Article

LA English

AB Members of the transforming growth factor beta1 (TGF-beta) superfamily—namely, TGF-beta and BMP2—applied to undifferentiated murine embryonic stem cells up-regulated mRNA of mesodermal (Brachyury) and cardiac specific transcription factors (Nkx2.5, MEF2C). Embryoid bodies generated from stem cells primed with these growth factors demonstrated an increased potential for cardiac differentiation with a significant increase in beating areas and enhanced myofibrillogenesis. In an environment of postmitotic cardiomyocytes, stem cells engineered to express a fluorescent protein under the control of a cardiac promoter differentiated into fluorescent ventricular myocytes beating in synchrony with host cells, a process significantly enhanced by TGF-beta or BMP2 *in vitro*. ***disruption*** of the TGF-beta/ ***BMP*** signaling pathways by latency-associated peptide and/or noggin prevented differentiation of stem cells. In fact, only host cells that secrete a TGF-beta family member induced a cardiac phenotype in stem cells *in vivo*. Transplantation of stem cells into heart also resulted in cardiac differentiation provided that TGF-beta/BMP2 signaling was intact. In infarcted myocardium, grafted stem cells differentiated into functional cardiomyocytes integrated with surrounding tissue, improving contractile performance. Thus, embryonic stem cells are directed to differentiate into cardiomyocytes by signaling mediated through TGF-beta/BMP2, a cardiac paracrine pathway required for therapeutic benefit of stem cell transplantation in diseased heart

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FILE 'BIOSIS_EMBASE_CAPLUS' ENTERED AT 11:06:21 ON 13 MAR 2003

L1 13855 S BONE MORPHOGENETIC PROTEIN? OR BMP
L2 11378 S BONE MORPHOGENETIC PROTEIN?
L3 1377 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DEL
L4 1139 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT?)
L5 871 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN?)
L6 501 S L1 AND (KNOCKOUT OR TRANSGEN?)
L7 258 S L1 (5A) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DE
L8 137 DUP REM L7 (121 DUPLICATES REMOVED)
L9 1625 S BMP-4
L10 174 S L9 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DE
L11 86 DUP REM L10 (88 DUPLICATES REMOVED)
L12 203 S L8 OR L11

=> s L9 (5a) (knockout or transgen? or deficien? or disrupt? or delet?)
L13 28 L9 (5A) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DE
DELET?)

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L14 13 DUP REM L13 (15 DUPLICATES REMOVED)

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L14 ANSWER 1 OF 13 BIOSIS COPYRIGHT 2003 ELSEVIER SCI B V
AN 2003071240 EMBASE
T Involvement of bone morphogenetic protein 4 (BMP-4) in pituitary prolactinoma pathogenesis through a Smad/estrogen receptor crosstalk.
AU Paez-Pereira M, Giacomini D, Reijo D, Nagashima A C, Hopfner U, Grubler Y, Chevrel A, Goldberg V, Goya R, Hentges S T, Low M J, Holisboer F, Stalla G K, Arzt E.

CS E Arzt, Departamento de Fisiologia, Universidad de Buenos Aires, Ciudad Universitaria, C1428EHA Buenos Aires, Germany. earzt@fbmc.uba.ar
SO Proceedings of the National Academy of Sciences of the United States of America, (4 Feb 2003) 100(3) 1034-1039.

Refs 45
ISSN 0027-8424 CODEN PNASA6

CY United States
DT Journal Article
FS 003 Endocrinology

005 General Pathology and Pathological Anatomy

LA English

SL English

AB Pituitary tumor development involves clonal expansion stimulated by hormones and growth factors/cytokines. Using mRNA differential display, we found that the bone morphogenetic protein (BMP) inhibitor noggin is down-regulated in pro adenomas from dopamine D2-receptor-***deficient*** mice. ***BMP*** - ***4*** is overexpressed in prolactinomas taken from dopamine D2-receptor-deficient female mice, but expression of the highly homologous BMP-2 does not differ in normal pituitary tissue and prolactinomas. BMP-4 is overexpressed in other prolactinoma models, including estradiol-induced rat prolactinomas and human prolactinomas, compared with normal tissue and other pituitary adenoma types (Western blot analysis of 48 tumors). BMP-4 stimulates, and noggin blocks, cell proliferation and the expression of c-Myc in human prolactinomas, whereas BMP-4 has no action in other human pituitary tumors. GH3 cells stably transfected with a dominant negative of Smad4 (Smad4dn, a BMP signal cotransducer) or noggin have reduced tumorigenicity in nude mice. Tumor growth is recovered in vivo when the Smad4dn expression was lost, proving that BMP-4/Smad4 are involved in tumor development in vivo. BMP-4 and estrogens act through overlapping intracellular signaling mechanisms on GH3 cell proliferation and c-myc expression; they had additive effects at low concentrations but not at saturating doses, and their action was inhibited by blocking either pathway with the reciprocal antagonist (i.e., BMP-4 with ICI 182780 or 17 beta-estradiol with Smad4dn). Furthermore, communoprecipitation studies demonstrate that under BMP-4 stimulation Smad4 and Smad1 physically interact with the estrogen receptor. This previously undescribed prolactinoma pathogenesis mechanism may participate in tumorigenicity in other cells where estrogens and the type beta transforming growth factor family have important roles.

L14 ANSWER 2 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS
INC DUPLICATE
1

AN 2002418048 BIOSIS
DN PREV200200418048

TI Ex vivo gene therapy with stromal cells transduced with retroviral vector containing the BMP4 gene completely heals critical size calvarial defect in rats

AU Gysin, R, Wergedal, J E, Sheng, M H-C, Kasukawa, Y, Miyakoshi, N, Chen, S-T, Peng, H, Lau, K-H W, Mohan, S, Baylink, D J (1)

CS (1) Musculoskeletal Disease Center, Jerry L Pettis Memorial VA Medical Center, 11201 Benton Street, 151, Loma Linda, CA, 92357 USA

SO Gene Therapy, (August, 2002) Vol. 9, No. 15, pp 991-999

<http://www.nature.com/gt/print>

ISSN 0969-7128

DT Article

LA English

AB In order to develop a successful gene therapy system for the healing of bone defects, we developed a murine leukemia virus (MLV)-based retroviral system expressing the human bone morphogenetic protein (***BMP***) ***4*** ***transgene*** with high transduction efficiency. The bone formation potential of BMP4 transduced stromal cells in a gelatin matrix that was then placed in a critical size defect in calvariae of syngenic rats. Gelatin matrix without cells or with untransduced stromal cells were the two control groups. The defect area was completely filled with new bone in experimental rats after 4 weeks, while limited bone formation occurred in either control group. Bone mineral density (BMD) of the defect in the gene therapy group was 67.8+/-5.7 mg/cm² (mean+/-s.d., n=4), which was 119+/-10% of the control BMD of bone surrounding the defect (57.2+/-1.5 mg/cm²). In contrast, BMD of rats implanted with untransduced stromal cells was five-fold lower (13.8+/-7.4 mg/cm², P<0.001). Time course studies revealed that there was a linear increase in BMD between 2-4 weeks after inoculation of the critical size defect with 2.5X10⁶ implanted BMP4 cells. In conclusion, the retroviral-based BMP4 gene therapy system that we have developed has the potential for regeneration of large skeletal defects

L14 ANSWER 3 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS
INC DUPLICATE

2

AN 200327391 BIOSIS

DN PREV200300027391

TI Transcriptional regulation of Xbr-1a/Xvent-2 homeobox gene: Analysis of its promoter region

AU Lee, Hyun-Shik, Park, Mae Ja, Lee, Sung-Young, Hwang, Yoo-Seok, Lee, Hyosang, Roh, Dong-Hyun, Kim, Jong-Il, Park, Jae-Bong, Lee, Jae-Yong, Kung, Hsiang-Fu, Kim, Jaebong (1)

CS (1) Department of Biochemistry, College of Medicine, Hallym University, Chuncheon, Gangwon-Do, 200-702, South Korea; jbkim@hallym.ac.kr South Korea

SO Biochemical and Biophysical Research Communications, (November 15 2002) Vol. 298, No. 5, pp. 815-823 print
ISSN: 0006-291X

DT Article

LA English

AB Xvent homeobox proteins are induced by BMP-4 signaling and have been known

to mediate many BMP-4 activities as key downstream transcriptional factors. In order to investigate the regulatory mode of Xvent transcription, we isolated genomic DNA of the Xbr-1a/Xvent-2 containing the promoter region responsive to BMP-4 signaling. The cis-acting elements located within the Xbr-1a/Xvent-2 promoter and the regulation modes by ***BMP*** - ***4*** signaling were analyzed by serial ***deletion*** and site-directed mutagenesis experiments. The upstream -235 bp of the promoter retained the full transcriptional activity and BMP-4-response when compared with the longest promoter construct. Further analysis indicated that two separated 15 bp regions contained a strong positive element and BMP-4-response element. Site-directed mutagenesis of those regions suggests that those two regions cooperate for the promoter activity and BMP-4-response. Moreover, we found that the transcription factors, Oaz and PEBP2alphaA, were able to elicit additive effects with BMP-4 signaling on Xbr-1a/Xvent-2 reporter activities. These results indicate that transcriptional regulation of the Xbr-1a/Xvent-2 gene occurs in a complex mode through the cooperation of various transcription factors.

L14 ANSWER 4 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS
INC DUPLICATE

3

AN 2002385185 BIOSIS

DN PREV200200385185

TI Zebrafish SPI-1 (PU 1) marks a site of myeloid development independent of primitive erythropoiesis: Implications for axial patterning

AU Lieschke, Graham J (1), Oates, Andrew C, Paw, Barry H, Thompson, Margaret A, Hall, Nathan E, Ward, Alister C, Ho, Robert K, Zon, Leonard I, Layton, Judith E

CS (1) Ludwig Institute for Cancer Research, The Royal Melbourne Hospital, Parkville, Victoria, 3050 Graham.Lieschke@ludwig.edu.au Australia

SO Chemical Research in Toxicology, (June 15, 2002) Vol. 24, No. 2, pp 274-295 <http://pubs.acs.org/journals/crtoec/> print
ISSN 0893-228X

DT Article

LA English

AB The mammalian transcription factor SPI-1 (synonyms: SPI1, PU 1, or Sfp1) plays a critical role in myeloid development. To examine early myeloid commitment in the zebrafish embryo, we isolated a gene from zebrafish that is a SPI-1 orthologue on the basis of homology and phylogenetic considerations. The zebrafish sp1 (pu1) gene was first expressed at 12 h postfertilization in rostral lateral plate mesoderm (LPM), anatomically isolated from erythroid development in caudal lateral plate mesoderm. Fate-mapping traced rostral LPM cells from the region of initial sp1 expression to a myeloid fate. sp1 expression was lost in the bloodless mutant cloche, but rostral sp1 expression and myeloid development were preserved in the mutant spadetail, despite its complete erythropoietic failure. This dissociation of myeloid and erythroid development was further explored in studies of embryos overexpressing ***BMP*** -

4, or chordin, in bmp- ***deficient*** swirl and snailhouse mutants, and chordin-deficient chordin mutants. These studies demonstrate that, in zebrafish, *sp1* marks a rostral population of LPM cells committed to a myeloid fate anatomically separated from and developmentally independent of erythroid commitment in the caudal LPM. Such complete anatomical and developmental dissociation of two hematopoietic lineages adds an interesting complexity to the understanding of vertebrate hematopoietic development and presents significant implications for the mechanisms regulating axial patterning.

L14 ANSWER 5 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2002 199018 BIOSIS

DN PREV200200199018

T1 Transcriptional activation of the GATA-2 gene by a Smad-dependent BMP signaling pathway

AU Evans, Todd (1), Oren, Tal (1), Schmerer, Matthew (1)

CS (1) Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, NY USA

SO Blood, (November 16, 2001) Vol. 98, No. 11 Part 1, pp. 553a-554a

http://www.bloodjournal.org/ print

Meeting Info: 43rd Annual Meeting of the American Society of Hematology, Part 1 Orlando, Florida, USA December 07-11, 2001

ISSN 0006-4971

DT Conference

LA English

AB Bone Morphogenetic Proteins (BMPs) are implicated in the development of embryonic ventral mesoderm, which includes the first progenitors of hematopoietic cells (the primitive lineage). In this study we investigate the mechanism by which BMP signaling regulates primitive blood differentiation. In *Xenopus*, the transcription factor GATA-2 is expressed in a pattern which precedes the development of the ventral blood islands, the frog homologue of mammalian yolk sac blood islands. We found that GATA-2 transcription is activated by exogenous BMP-4 and have now established a reporter assay that allows analysis of GATA-2 transcriptional activation during embryonic development. By injecting a GATA-2 promoter reporter plasmid into *Xenopus* embryos we demonstrate that the GATA-2 promoter is activated by both an endogenous embryonic program and induced further by forced expression of ***BMP*** - ***4***.

Deletion analysis of the GATA-2 promoter identified a 68 bp BMP-4 responsive element (BRE). This BRE maps approximately 750 bp upstream of the transcriptional start site, and gel mobility-shift assays were used to identify protein complexes that interact specifically with this sequence. We present data describing the essential sequences of the BRE and a biochemical analysis of proteins that mediate activation through the BRE. Among the candidates are Smad proteins, known to be downstream transducers of the BMP-4 signal. Injection of an inhibitory Smad (Smad-6), blocks activation of the GATA-2 reporter in response to BMP-4. An estrogen-inducible isoform of Smad-6 was used to show that endogenous BMP signaling is required after gastrulation in ventral tissues for normal blood island differentiation. In sum, our results argue that activation of the GATA-2 promoter is Smad-dependent, and that a BMP signaling pathway converges on a specific regulatory region of the GATA-2 gene as a necessary component of embryonic (primitive) hematopoiesis.

L14 ANSWER 6 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2001 567333 BIOSIS

DN PREV200100567333

T Partial rescue of the embryonic lethal phenotype of the ***BMP*** - ***4*** ***knockout*** with a 1 kb proximal BMP-4 promoter region

AU Feng, J. Q. (1), Zhang, J., Harris, M., Tan, X., Pi, Y., Harris, S. E. CS (1) Oral Biology, School of Dentistry, Univ. of Missouri-Kansas City, Kansas City, MO USA

SO Journal of Bone and Mineral Research, (September, 2001) Vol. 16, No. Suppl 1, pp. S438 print

Meeting Info: Twenty-Third Annual Meeting of the American Society for Bone and Mineral Research Phoenix, Arizona, USA October 12-16, 2001

ISSN 0884-0431

DT Conference

LA English

SL English

L14 ANSWER 7 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC DUPLICATE

4

AN 2000 227217 BIOSIS

DN PREV200000227217

T Characterization of the functionally related sites in the neural inducing gene noggin

AU Liu, Weidong, Ren, Caiping, Shi, Jianling, Feng, Xiangling, He, Zhiwei, Xu, Liangguo, Lan, Ke, Xie, Lu, Peng, Ying, Fan, Jing, Fung, Hsiang-tu, Yao, Kai-Tai (1), Xu, Ren-He

CS (1) Department of Pathology, First Military Medical University, Guangzhou, 510515 China

SO Biochemical and Biophysical Research Communications, (April 2, 2000) Vol. 270, No. 1, pp. 293-297

ISSN 0006-291X

DT Article

LA English

SL English

AB Previously we have shown that blocking bone morphogenetic protein (BMP) receptor signaling by a dominant negative BMP receptor causes neurogenesis

in *Xenopus* animal caps (ACs), whereas the physiological neural inducer noggin acts as a homodimer physically binding to ***BMP*** - ***4*** and ***disrupting*** its signaling at the ligand level. The present study attempted to elucidate the relationship between the structure and function of noggin. By replacing some cysteine residues with serine residues through a site-directed mutagenesis strategy, we generated three noggin mutants, C145S, C205S, and C(218, 220, 222)S (3CS). Although mRNAs

encoded by these mutants were translated as efficiently as wild-type (WT) noggin mRNA, they behaved differently when expressed in vivo. Expression of WT noggin or C205S in *Xenopus* ACs converted the explants (prospective ectoderm) into neural tissue, indicated by the neural-like morphology and expression of the pan neural marker NCAM in the ACs. In contrast, ACs expressing C145S or 3CS sustained an epidermal fate like the control caps. Similar results were observed in the mesoderm where C205S (but not C145S and 3CS) displayed dorsalizing activity as well as WT noggin. Altogether, our results suggest that Cys145 alone or Cys(218, 220, 222) as a whole in noggin protein is required for the biological activities of noggin, probably participating in the dimerization of noggin with BMP-4 or itself.

L14 ANSWER 8 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI

BV DUPLICATE 5

AN 1999002833 EMBASE

T1 Mitogen-activated protein kinase and neural specification in *Xenopus*

AU Uzgare A. R., Uzman J. A., El-Hodin H. M., Sater A. K.

CS (1) K. Sater, Department of Biology, University of Houston, Houston, TX 77224-5513, United States. asater@jetson.uh.edu

SO Proceedings of the National Academy of Sciences of the United States of America, (1998) 95/25 (14833-14838)

Revs. 55

ISSN: 0027-8424 CODEN: PNASAB

CY United States

DT Journal, Article

FS 021 Developmental Biology and Teratology

C29 Clinical Biochemistry

LA English

SL English

AB We have investigated the activity and function of mitogen-activated protein kinase (MAPK) during neural specification in *Xenopus*. Ectodermal MAPK activity increased between late blastula and midgastrula stages. At midgastrula, MAPK activity in both newly induced neural ectoderm and ectoderm overexpressing the anterior neural inducer noggin was 5-fold higher than in uninduced ectoderm. Overexpression of MAPK phosphatase-1 (MKP-1) in ectoderm inhibited MAPK activity and prevented neurectoderm-specific gene expression when the ectoderm was recombined with dorsal mesoderm or treated with fibroblast growth factor (FGF). Neurectoderm-specific gene expression was observed, however, in ectoderm overexpressing both noggin and MKP-1. To evaluate the role of MAPK in posterior regionalization, ectodermal isolates were treated with increasing concentrations of FGF and assayed for MAPK activity and neurectoderm-specific gene expression. Although induction of posterior neural ectoderm by FGF was accompanied by an elevation of MAPK activity, relative MAPK activity associated with posterior neural fate was no higher than that of ectoderm specified to adopt an anterior neural fate. Thus, increasingly posterior neural fates are not correlated with quantitative increases in MAPK activity. Because MAPK has been shown to down-regulate Smad1, MAPK may ***disrupt*** bone morphogenetic protein 4 (***BMP*** - ***4***) signaling during neural specification. Our results suggest that MAPK plays an essential role in the establishment of neural fate in vivo.

L14 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC DUPLICATE

6

AN 1998 208314 BIOSIS

DN PREV199800208314

T1 *Xenopus* Smad8 acts downstream of BMP-4 to modulate its activity during vertebrate embryonic patterning

AU Nakayama, Takuwa, Snyder, Mark A., Grewal, Savraj S., Tsuneizumi, Kazuhide, Tabata, Tetsuya, Christian, Jan L. (1)

CS (1) Dep. Cell Dev. Biol., L215, Oregon Health Sci. Univ., Sch. Med., 3181 SW Sam Jackson Park Rd., Portland, OR 97201-3098 USA

SO Development (Cambridge), (March, 1998) Vol. 125, No. 5, pp. 857-867

ISSN: 0950-1991

DT Article

LA English

AB Bone morphogenetic proteins (BMPs) participate in the development of nearly all organs and tissues. BMP signaling is mediated by specific Smad proteins, Smad1 and/or Smad5, which undergo serine phosphorylation in response to BMP-receptor activation and are then translocated to the nucleus where they modulate transcription of target genes. We have identified a distantly related member of the *Xenopus* Smad family, Smad8, which lacks the C-terminal SSXS phosphorylation motif present in other Smads, and which appears to function in the BMP signaling pathway. During embryonic development, the spatial pattern of expression of Smad8 mirrors that of BMP-4. We show that an intact BMP signaling pathway is required for its expression. Overexpression of Smad8 in *Xenopus* embryos phenocopies the effect of blocking BMP4 signaling, leading to induction of a secondary axis on the ventral side of intact embryos and to direct neural induction in ectodermal explants. Furthermore, Smad8 can block BMP-4-mediated induction of ventral mesoderm-specific gene expression in ectodermal explants. Overexpression of Smad8 within dorsal cells, however, causes patterning defects that are distinct from those reported in ***BMP*** - ***4***.

4 - ***deficient*** embryos, suggesting that Smad8 may interact with additional signaling pathways. Indeed, overexpression of Smad8 blocks expression of Xbra in whole animals, and partially blocks activin signaling in animal caps. In addition, Smad8 inhibits involution of mesodermal cells during gastrulation, a phenotype that is not observed following blockade of activin or BMPs in *Xenopus*. Together, these results are consistent with the hypothesis that Smad8 participates in a negative feedback loop in which BMP signaling induces the expression of Smad8, which then functions to negatively modulate the amplitude or duration of signaling downstream of BMPs and, possibly, downstream of other transforming growth factor-beta (TGF-beta) family ligands.

L14 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC DUPLICATE

7
AN 1995 255921 BIOSIS
CN PREV199598270221
T1 Chemical skin carcinogenesis is prevented in mice by the induced expression of a TGF-beta related transgene
AU Blessing, Manfed (1); Nanney, Lillian B.; King, Lloyd E.; Hogan, Brigid L. M.
CS (1) I. Med Klinik, Poliklinik, Johannes Gutenberg-Univ., Mainz Germany
SO Teratogenesis Carcinogenesis and Mutagenesis, (1995) Vol. 15, No. 1, pp 11-21.
ISSN 0270-3211
DT Article
LA English
AB Skin papillomas and squamous cell carcinomas (SCCs) are induced in mice by tumor initiation with a carcinogen followed by tumor promotion with the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA). These usually arise from preneoplastic lesions characterized by epidermal proliferation and hyperplasia, dermal edema, and inflammation. To evaluate the role of polypeptide growth factors in chemically induced skin carcinogenesis, we used transgenic mice carrying the cDNA for a TGF-beta related molecule, bone morphogenetic protein-4 (BMP-4), under the control of the regulatory elements of the cytokeratin IV gene in a skin carcinogenesis protocol. Control non-***transgenic*** littermates and ***BMP*** - ***4*** ***transgenic*** mice were treated with a single dose of a carcinogen, N-methyl-N-nitrosoguanidine (MNNG), and biweekly with the tumor promoter TPA for 9 months. In control littermates TPA induced epidermal hyperproliferation, atypia with "dark" cells, and dermal inflammation, resulting in papillomas and SCCs in 13 of 26 animals tested. In ***BMP*** - ***4*** ***transgenic*** mice, TPA treatment induced the expression of the ***BMP*** - ***4*** ***transgene*** in interfollicular epidermis but only minimal epidermal thickening, hyperproliferation, and inflammation were noted after the initial dose of TPA. Furthermore, the mitotic indices in transgenic epidermis after 9 months of TPA treatment were significantly lower than the corresponding indices from untreated transgenic epidermis. Consequently, none of the 22 transgenic animals tested developed papillomas or SCCs. In conclusion, we have shown that the TPA induced expression of the ***BMP*** - ***4*** ***transgene*** blocks proliferation and inflammation in skin, steps that are critical to the subsequent formation of papillomas and SCCs and we characterized an inducible promotersystem which expresses polypeptides in interfollicular epidermis after exogenous stimulation.

L14 ANSWER 11 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI

B V DUPLICATE 8
AN 94331598 EMBASE
DN 1994331598
T Bone and cartilage differentiation
AU Reddi, A. H.
CS Department of Orthopaedic Surgery, Johns Hopkins Univ School Medicine, Ross Research Building 225, 720 Rutland Avenue, Baltimore, MD 21205-2196, United States
SO Current Opinion in Genetics and Development, (1994) 4/5 (737-744). ISSN 0959-437X CODEN COGDET
CY United Kingdom
DT Journal, General Review
FS 021 Developmental Biology and Teratology
LA English
SL English
AB Recent progress in the study of regulation of bone and cartilage differentiation has come from the isolation, cloning, and expression of genes encoding bone morphogenetic proteins (BMPs). BMPs initiate cartilage and bone formation in a sequential cascade. Their pleiotropic effects on chemotaxis, mitosis, and differentiation are based on concentration-dependent thresholds. The existence of multiple members of the BMP family raises issues concerning functional redundancy. Current work in progress in different laboratories has revealed that BMP-2 or ***BMP*** - ***4*** ***knockout*** by homologous recombination results, surprisingly, in embryonic lethality. Cartilage and bone differentiation during endochondral development involves a continuum of steps: initiation, promotion, maintenance, modeling, and termination. The signaling factors for initiation and maintenance are being defined at the molecular level, and future studies will focus on the gene regulation of initial signaling molecules such as BMPs. Critical progress in the determination of the role of BMPs in bone development has been accomplished by systematic study of skeletal mutants such as short ear and brachyptism in mice. The accelerating pace of advance in this area augurs well for the resolution of the molecular basis of morphogenesis of bone and cartilage.

L14 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2003 ACS
AN 1993 464927 CAPLUS
DN 119 64927

T1 Recombinant bone morphogenetic protein heterodimers and their manufacture with transgenic cells

IN Israel, David; Wolfman, Neil M
PA Genetics Institute, Inc., USA
SO PCT Int. Appl. 168 pp
CODEN PIXXD2

DT Patent

LA English

FAN CNT 2

PATENT NO. KIND DATE APPLICATION NO. DATE

PI WO 9309229 A1 19930513 WO 1992-US9430 19921102

W AU, BR, CA, FI, HU, JP, KR, NO, RU

RW AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE

AU 9230622 A1 19930607 AU 1992-30622 19921102

AU 674500 B2 19970102

EP 612348 A1 19940831 EP 1992-924237 19921102

R AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, SE

US 5866364 A 19990202 US 1992-989847 19921127

US 6190880 B1 20010220 US 1995-469411 19950606

PRA US 1991-787496 A 19911104

US 1992-864692 A 19920407

WO 1992-US9430 A 19921102

US 1992-989847 A 19921127

AB A method for producing heterodimeric bone morphogenetic proteins (BMPs) comprises culturing a transgenic cell expressing 2 different BMP genes and isolating the heterodimeric BMP from the medium. CHO cells cotransfected with plasmids encoding BMP-2 or BMP-4 and with plasmids encoding BMP-5, BMP-6 or BMP-7 produced heterodimeric BMPs. These heterodimers stimulated W20 cells to produce more alkaline phosphatase activity than did the individual BMP homodimers or mixts. of homodimers. The heterodimers also performed better in an in vivo test, the rat ectopic bone formation assays.

L14 ANSWER 13 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC DUPLICATE

9

AN 1993 229420 BIOSIS

DN PREV19935120595

T1 Transgenic mice as a model to study the role of TGF-beta-related molecules in hair follicles

AU Blessing, Manfed (1); Nanney, Lillian B.; King, Lloyd E.; Jones, C.

Michael; Hogan, Brigid L. M.

CS (1) Dep Cell Biol, Vanderbilt Univ. Sch. Med., Nashville, TN 37232 USA

SO Genes & Development, (1993) Vol. 7, No. 2, pp 204-215.

ISSN: 0890-9369.

DT Article

LA English

AB There is increasing evidence that members of the TGF-beta superfamily are important regulators of epithelial growth and differentiation in vivo. Here, transgenic mice have been used to study the role of the TGF-beta-related growth factors BMP-2 and BMP-4 in hair and whisker development. In the mature hair follicle, 3MP-2 transcripts are normally seen only in preortex cells at the base of the hair shaft. In the ***transgenic*** mice reported here, ***BMP*** - ***4***, a closely related molecule, has been ectopically expressed in the outer root sheath of hair and whisker follicles using an expression vector based on the bovine cytokeratin IV promoter. In response to transgene expression, both outer root sheath cells below the stem cell compartment and hair matrix cells around the dermal papilla cease proliferation. In addition, the expression pattern of cytokeratin markers is disturbed in some transgenic hair follicles. These results support a model in which members of the TGF-beta superfamily play an active role in the inhibition of cell proliferation and the onset of expression of trichocyte-specific genes that take place when cells leave the matrix of the follicle and differentiate into shaft cells.

=> d his

(FILE 'HOME' ENTERED AT '1 05 42 ON 13 MAR 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11 06 21 ON 13 MAR 2003

L1 13855 S BONE MORPHOGENETIC PROTEIN? OR BMP

L2 11378 S BONE MORPHOGENETIC PROTEIN?

L3 1377 S L1 AND (K NOCK OUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DEL

L4 1139 S L1 AND (K NOCK OUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT?)

L5 871 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN?)

L6 501 S L1 AND (KNOCKOUT OR TRANSGEN?)

L7 258 S L1 (5A) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT?) OR DE

L8 137 DUP REM L7 (121 DUPLICATES REMOVED)

L9 1625 S BMP-4

L10 174 S L9 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT?) OR DE

L11 86 DUP REM L10 (88 DUPLICATES REMOVED)

L12 203 S L8 OR L11

L13 28 S L9 (5A) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR D
L14 13 DUP REM L13 (15 DUPLICATES REMOVED)

=> s18 not l14
L15 126 L8 NOT L14

=> s18 and py<=2000
1 FILES SEARCHED
L16 73 L8 AND PY<=2000

=> d bib abs 1-20

L16 ANSWER 1 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2001 91549 BIOSIS

DN PREV200100091549

TI Cardiac-specific deletion of ALK3, the type IA receptor for bone morphogenetic proteins, unmasks an essential, myocyte-autonomous role in the mid gestation heart.

AU Gauvin, Vinciane (1); Van de Putte, Tom; Mishina, Yuji; Zwijnen, An; Huylebroeck, Danny; Behringer, Richard R.; Schneider, Michael D.

CS (1); Penn State College of Medicine/Weis Center for Research, Hershey, PA USA

SO Basic Research in Cardiology, (***December, 2000***) Vol. 95, No. 6, pp 528 print.
Meeting Info.: 2nd International Amsterdam Symposium on the Cardiovascular Physiology of Mice Amsterdam, Netherlands April 13-15, 2000

ISSN: 0300-8428

DT Conference

LA English

SL English

L16 ANSWER 2 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2001 84627 BIOSIS

DN PREV200100084627

TI Sporadic primary pulmonary hypertension is associated with germline mutations of the gene encoding BMPR-II, a receptor member of the TGF-beta family.

AU Thomson, J R (1); Machado, R D (1); Morgan, N V (1); Loyd, J E; Nichols, W C; Trembath, R C (1)

CS (1); Division of Medical Genetics, University of Leicester, Leicester, LE1 7RH UK

SO Thorax, (***December, 2000***) Vol. 55, No. Supplement 3, pp. A23. print.
Meeting Info.: Winter Meeting of the British Thoracic Society Westminster, London, UK December 13-15, 2000 British Thoracic Society
ISSN: 0040-6376

DT Conference

LA English

SL English

L16 ANSWER 3 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2001 84626 BIOSIS

DN PREV200100084626

TI Heterozygous germline mutations in BMPR2, encoding a TGF-beta receptor, cause familial primary pulmonary hypertension

AU Machado, R D (1); Thomson, J R (1); Loyd, J E; Nichols, W C; Trembath, R C (1); International PPH Consortium (1)

CS (1); Division of Medical Genetics, University of Leicester, Leicester, LE1 7RH UK

SO Thorax, (***December, 2000***) Vol. 55, No. Supplement 3, pp. A23. print.
Meeting Info.: Winter Meeting of the British Thoracic Society Westminster, London, UK December 13-15, 2000 British Thoracic Society
ISSN: 0040-6376

DT Conference

LA English

SL English

L16 ANSWER 4 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2001 72075 BIOSIS

DN PREV200100072075

TI Inhibition of Bmp signaling affects growth and differentiation in the anagen hair follicle

AU Kulessa, Holger; Turk, Gail; Hogan, Brigid L. M. (1)

CS (1); Howard Hughes Medical Institute and Department of Cell Biology, Vanderbilt University Medical Center, Nashville, TN; brigid.hogan@mcmill.vanderbilt.edu USA

SO EMBO (European Molecular Biology Organization) Journal, (***December 15*** *** 2000***) Vol. 19, No. 24, pp. 6664-6674 print
ISSN: 0261-4189

DT Article

LA English

SL English

AB Growth and differentiation of postnatal hair follicles are controlled by reciprocal interactions between the dermal papilla and the surrounding epidermal hair precursors. The molecular nature of these interactions is largely unknown, but they are likely to involve several families of

signaling molecules, including Fgfs, Wnts and Bmps. To analyze the function of Bmp signaling in postnatal hair development, we have generated ***transgenic*** mice expressing the ***Bmp*** inhibitor, Noggin, under the control of the proximal Msx2 promoter, which drives expression in proliferating hair matrix cells and differentiating hair precursor cells. Differentiation of the hair shaft but not the inner root sheath is severely impaired in Msx2-Noggin transgenic mice. In addition to hair keratins, the expression of several transcription factors implicated in hair development, including Foxn1 and Hoxc13, is severely reduced in the transgenic hair follicles. Proliferating cells, which are normally restricted to the hair matrix surrounding the dermal papilla, are found in the precortex and hair shaft region. These results identify Bmps as key regulators of the genetic program controlling hair shaft differentiation in postnatal hair follicles.

L16 ANSWER 5 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2001 68569 BIOSIS

DN PREV200100068569

TI Cardiac-specific deletion of ALK3, the type IA receptor for bone morphogenetic proteins, unmasks an essential, myocyte-autonomous role in the midgestation heart.

AU Gauvin, Vinciane (1); Van de Putte, Tom; Mishina, Yuji; Zwijnen, An; Huylebroeck, Danny; Behringer, Richard R.; Schneider, Michael D.

CS (1); Penn State College of Medicine, Danville, PA USA

SO Circulation, (***October 31, 2000***) Vol. 102, No. 18 Supplement, pp. II-112. print.
Meeting Info.: Abstracts from Scientific Sessions 2000 New Orleans, Louisiana, USA November 12-15, 2000
ISSN: 0009-7322

DT Conference

LA English

SL English

L16 ANSWER 6 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2001 32529 BIOSIS

DN PREV200100032529

TI Mesenchymal/epithelial induction mediates olfactory pathway formation

AU LaManta, Anthony-Samuel (1); Bhasin, Naina; Rhodes, Katton; Heemskerk, Jill

CS (1); Department of Cell and Molecular Physiology and Center for Neuroscience, The University of North Carolina at Chapel Hill, Medical School, Chapel Hill, NC, 27599 anthony_lamanta@med.unc.edu USA

SO Neuron, (***November, 2000***) Vol. 28, No. 2, pp. 411-425 print
ISSN: 0896-6273

DT Article

LA English

SL English

AB In the olfactory pathway, as in the limbs, branchial arches, and heart, mesenchymal/epithelial induction, mediated by retinoic acid (RA) FGF8, sonic hedgehog (shh), and the BMPs, defines patterning, morphogenesis, and differentiation. Neuronal differentiation in the olfactory epithelium and directed growth of axons in the nascent olfactory nerve depend critically upon this inductive interaction. When RA, FGF8, shh, or ***BMP*** signaling is ***disrupted***, distinct aspects of olfactory pathway patterning and differentiation are compromised. Thus, a cellular and molecular mechanism that facilitates musculoskeletal and vascular development elsewhere in the embryo has been adapted to guide the differentiation of the olfactory pathway in the developing forebrain.

L16 ANSWER 7 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2001 23926 BIOSIS

DN PREV200100023926

TI Regulation of the promoters for the human bone morphogenetic protein 2 and 4 genes

AU Helvering, Leah M. (1); Sharp, Robert L.; Ou, Xuemei; Geiser, Andrew G; CS (1); Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285 lhelvering@lilly.com USA

SO Gene (Amsterdam), (***3 October, 2000***) Vol. 256, No. 1-2, pp. 123-138. print
ISSN: 0378-1119

DT Article

LA English

SL English

AB The bone morphogenetic proteins 2 and 4 are known to be important in bone formation and are expressed in both the developing and adult mammalian bone. Understanding the regulation of these genes in osteoblasts may yield methods by which we can control expression to induce bone formation. We have isolated and characterized the human BMP-2 and BMP-4 promoters and report substantially more upstream sequence information than that which has been published. Human osteoblasts were found to have a single transcript initiation site that is conserved across species, rather than multiple start sites, as has previously been reported (Feng, J. Q.; Harris, M. A.; Ghosh-Choudhury, N.; Feng, M.; Mundy, G. R.; Harris, S. E., 1994. Structure and sequence of mouse morphogenetic protein-2 gene (BMP-2) comparison of the structures and promoter regions of BMP-2 and BMP-4 genes. *Biochim. Biophys. Acta* 1218, 221-224; Heller, L. C.; Li, Y.; Abrams, K. L.; Rogers, M. B., 1999. Transcriptional regulation of the Bmp2 gene. *J. Biol. Chem.* 274, 1394-1400; Sugiyama, T., 1999. Cloning and functional characterization of the 5'-flanking region of the human bone morphogenetic protein-2 gene. *Biochim. J.* 338, 433-440) A series of promoter

deletions for both human ***BMP*** -2 and BMP-4 fused to the luciferase reporter gene were analyzed thoroughly in human and murine osteoblastic cell lines. Several compounds and growth factors that stimulate general or osteogenic pathways were used to treat cells transfected with the promoter constructs. Retinoic acid compounds and the phorbol ester, PMA were found to stimulate BMP-2 and, to a lesser degree, BMP-4. The combination of all trans-RA and PMA caused a synergistic increase in BMP-2 promoter activity and endogenous mRNA. The RA stimulation appears to be an indirect effect on the BMP-2 promoter, as the most highly conserved RRE in the BMP-2 promoter was unable to functionally bind or compete for protein binding. Potential binding sites in both promoters for the bone-specific transcription factor, Cbfa-1, were found to specifically bind Cbfa-1 protein in osteoblast nuclear extracts; however, deletion of these sites did not significantly affect transcriptional activity of the promoters in osteoblasts. These data thus present new sequence and regulatory information for the human BMP-2 and BMP-4 promoters and clarify the human BMP-2 gene transcriptional start site in osteoblasts.

L16 ANSWER 8 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2000 535440 BIOSIS
DN PREV200000535440

Ti Nodal and bone morphogenetic protein 5 interact in murine mesoderm formation and implantation.
AU Pfendler, Kristina C., Yoon, JoonWon; Taborn, Gregory U.; Kuehn, Michael R.; Iannaccone, Philip M. (1)
CS (1) Department of Pediatrics, Northwestern University Medical School and Developmental Biology Program of the Children's Memorial Institute for Education and Research, Children's Memorial Hospital, 2300 Children's Plaza, Chicago, IL, 60614 USA
SO Genesis The Journal of Genetics and Development, (***September, 2000***) Vol. 28, No. 1, pp. 1-14 print
ISSN 1526-954X

DT Article

LA English

SL English

AB Mice mutant for the TGF-beta family member, nodal, lack mesoderm and die between E8.5 and E9.5. The short ear-lethal (sel) mutation, a ***deletion*** that eliminates ***Bmp*** -5, causes a strikingly similar gastrulation defect. Here we analyze sel; nodal compound mutants and find a dosage effect. Embryos homozygous for one mutation show distinct gastrulation stage defects that depend on whether they are heterozygous or homozygous for the other mutation. Embryos mutant for nodal or sel; nodal compound mutants fail to execute an antigenic shift indicative of mesoderm differentiation and ectoderm cells are shunted into an apoptotic pathway. Furthermore, we find a novel phenotype in sel; nodal double mutant litters, in which two to four genetically different embryos are contained within the same deciduum. Both the gastrulation and implantation phenotypes can also arise in short ear-viable (sev) and sev; nodal mutant mice. These data indicate that loss of Bmp-5 may underlie the sel gastrulation phenotype and suggest that nodal and Bmp-5 interact during murine mesoderm formation. Our data also reveal an unsuspected role for Bmp-5 in implantation and the decidual response in the mouse.

L16 ANSWER 9 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2000 450689 BIOSIS
DN PREV200000450689

T Breast hypoplasia and disproportionate short stature in the ear, patella, short stature syndrome: Expansion of the phenotype.
AU Terhal, P. A. (1); Ausems, M. G. E. M.; Van Bever, Y.; Ten Kate, L. P.; Dijkstra, P. F.; Kuipers, G. M. C.
CS (1) Department of Medical Genetics, University Medical Centre Utrecht, Utrecht Netherlands
SO Journal of Medical Genetics, (***September, 2000***) Vol. 37, No. 9, pp. 719-721 print
ISSN 0022-2593

DT Article, Letter

LA English

SL English

L16 ANSWER 10 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2000 431295 BIOSIS
DN PREV200000431295

T glycan-3 controls cellular responses to Bmp4 in limb patterning and skeletal development.
AU Paine-Saunders, Stephenie, Viviano, Beth L.; Zupicich, Joel; Skarnes, William C.; Saunders, Scott (1)
CS (1) Washington University School of Medicine, 660 South Euclid Avenue, Saint Louis, MO, 63110 USA
SO Developmental Biology, (***September, 2000***) Vol. 225, No. 1, pp. 179-187 print
ISSN 0012-1606

DT Article

LA English

SL English

AB Glycans represent a family of six cell surface heparan sulfate proteoglycans in vertebrates. Although no specific in vivo functions have thus far been described for these proteoglycans, spontaneous mutations in the human and induced deletions in the mouse glycan-3 (Gpc3) gene result in severe malformations and both pre- and postnatal overgrowth, known

clinically as the Simpson-Golabi-Behmel syndrome (SGBS). Mice carrying mutant alleles of Gpc3 created by either targeted gene disruption or gene trapping display a wide range of phenotypes associated with SGBS including renal cystic dysplasia, ventral wall defects, and skeletal abnormalities that are consistent with the pattern of Gpc3 expression in the mouse embryo. Previous studies in *Drosophila* have implicated glycans in the signaling of decapentaplegic, a BMP homolog. Our experiments with mice show a significant relationship between vertebrate ***BMP*** signaling and glycan function. GPC3 ***deficient*** animals were mated with mice haploinsufficient for bone morphogenetic protein-4 (Bmp4) and their offspring displayed a high penetrance of postaxial polydactyly and rib malformations not observed in either parent strain. This previously unknown link between glycan-3 and BMP4 function provides evidence of a role for glycans in vertebrate limb patterning and skeletal development and suggests a mechanism for the skeletal defects seen in SGBS.

L16 ANSWER 11 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2000 353740 BIOSIS
DN PREV200000353740

T Ectopic BMPs disrupts chick telencephalic development through the repression of Shh and Fgf8 gene expression and the regulation of apoptosis.

AU Ohkubo, Yasushi (1); Rubenstein, John L. R. (1)

CS (1) Nina Ireland Lab., LPP1, UCSF, San Francisco, CA, 94143-0984 USA

SO Developmental Biology, (***June 1, 2000***) Vol. 222, No. 1, pp. 257- print
Meeting Info.: Fifty-ninth Annual Meeting of the Society for Developmental Biology Boulder, Colorado, USA June 07-11, 2000 Society for Developmental Biology
ISSN 0012-1606

DT Conference

LA English

SL English

L16 ANSWER 12 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2000 353293 BIOSIS
DN PREV200000353293

T Multilineage differentiation of Cbfa1-deficient calvarial cells in vitro

AU Kobayashi, Hirohiko; Gao, Yu-hao; Ueta, Chisato; Yamaguchi, Akira; Komori, Toshihisa (1)
CS (1) Department of Molecular Medicine, Osaka University Medical School, 2-2 Yamada-oka, Suita, Osaka, 565-0871 Japan
SO Biochemical and Biophysical Research Communications, (***July 5, 2000***) Vol. 273, No. 2, pp. 630-636 print
ISSN 0006-291X

DT Article

LA English

SL English

AB We characterized calvaria-derived cells of Cbfa1-deficient mice to determine their stages of differentiation. In long-term culture, Cbfa1-deficient calvarial cells did not acquire osteoblastic phenotypes, but numerous adipocyte foci appeared with an increase in the expression of marker genes for adipocyte differentiation. In culture with ***BMP*** -2, Cbfa1- ***deficient*** calvarial cells still failed to generate bone nodules but differentiated into chondrocytes and further to terminal hypertrophic chondrocytes, and adipocyte foci were decreased. Cbfa1-deficient calvarial cells transplanted into the peritoneal cavity of athymic mice using BMP-2-coated diffusion chambers generated cartilage but not bone. These data indicate that Cbfa1-deficient calvarial cells completely lack the ability to differentiate into mature osteoblasts and Cbfa1 has an inhibitory function in adipocyte differentiation. As Cbfa1-deficient calvarial cells were enriched with immature mesenchymal cells, which can differentiate into adipocytes and chondrocytes, it is suggested that Cbfa1 plays an essential role in determining the lineage of multipotential mesenchymal precursor cells.

L16 ANSWER 13 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 2000 334660 BIOSIS
DN PREV200000334660

T Slug is an essential target of TGFbeta2 signaling in the developing chicken heart.

AU Romano, Laura A.; Runyan, Raymond B. (1)

CS (1) Department of Cell Biology and Anatomy, University of Arizona, Tucson, AZ, 85724 USA
SO Developmental Biology, (***July 1, 2000***) Vol. 223, No. 1, pp. 91-102 print
ISSN 0012-1606

DT Article

LA English

SL English

AB An epithelial-mesenchymal cell transformation (EMT) occurs during the development of endocardial cushions in the atrioventricular (AV) canal of the heart. This is a complex developmental process regulated by multiple extracellular signals and signal transduction pathways. It was recently shown that the transcription factor Slug is expressed in the AV canal and is required for initial steps of EMT. Treatment of AV canal explants with either antisense oligodeoxynucleotides toward Slug or anti-TGFbeta2 antibody inhibited initial steps of EMT. Others have identified roles for HGF and BMP during EMT in the heart. Both HGF and BMP are known to regulate Slug in other cell types. To determine whether TGFbeta2 or other

signaling factors regulate Slug expression during EMT in the heart, we cultured AV canal explants in the presence of anti-TGFbeta2 antibody, anti-TGFbeta3 antibody, pertussis toxin, retinoic acid, noggin, or anti-HGF antibody. Only treatment with anti-TGFbeta2 antibody or retinoic acid inhibited Slug expression in AV canal explants. Consistent with these data, we found that retinoic acid disrupted initial steps of EMT, while antagonists of ***BMP*** and HGF signaling ***disrupted*** later steps of EMT. Transfection of AV canal explants with Slug rescued the inhibitory effect of anti-TGFbeta2 antibody but not retinoic acid on EMT. Slug is thus an essential target of TGFbeta2 signaling during EMT in the developing chicken heart.

L16 ANSWER 14 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2000 309387 BIOSIS
DN PREV200000309387

TI Heterotopic ossification of degenerating rat skeletal muscle induced by adenovirus-mediated transfer of bone morphogenetic protein-2 gene
AU Gonda, K. (1); Nakao, T.; Yoshimura, K.; Otawara-Hamamoto, Y.; Hara, K.
CS (1) Department of Plastic and Reconstructive Surgery, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan
SO Journal of Bone and Mineral Research, (***June, 2000***) Vol 15, No 6, pp 1056-1065, prnt
ISSN 0884-0431

DT Article
LA English
SL English

AB In vivo gene transfer is a recently developed device for efficient delivery of a therapeutic recombinant protein. We formulated the hypothesis that a high level of expression of bone morphogenetic protein 2 (BMP-2) could be a future therapeutic modality in terms of inducing substantial bone formation in vivo. First, to test this hypothesis, adenoviruses carrying BMP-2 gene were directly injected into the soleus muscle of adult rat. The BMP-2 gene was successfully overexpressed in the target muscle by adenovirus-mediated transfer, whereas bone formation in and around the muscle failed to occur in this case. Second, to recruit putative osteoprogenitor cells, we then induced ischemic degeneration of the target muscle by orthotopically grafting it simultaneously with the gene transfer. The combination of BMP-2 gene transfer and orthotopic muscle grafting resulted in successful ossification of almost the whole grafted muscle, whereas neither muscle grafting alone nor the combination of muscle grafting and adenovirus-mediated transfer of reporter gene LacZ induced any bone formation in the muscle. The ossification process was evident by positive von Kossa staining of the histological sections and roentgenographical radio-opacity of the region. It was also found that the ***BMP***-2 ***transgene*** overexpressed in grafted muscles inhibited muscle regeneration, which should otherwise follow the muscle degeneration. We further demonstrated an up-regulation of BMP receptor type IA in grafted muscles, suggesting its involvement in the bone-formation process. In conclusion, overexpression of BMP-2 gene induced massive heterotopic ossification in skeletal muscles under graft-induced ischemic degeneration, which possibly up-regulates osteoprogenitor cells in situ.

L16 ANSWER 15 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2000 227217 BIOSIS
DN PREV200000227217

TI Characterization of the functionally related sites in the neural inducing gene noggin
AU Liu, Weidong; Ren, Caiping; Shi, Jianling; Feng, Xiangling; He, Zhiwei; Xu, Liangguo; Lan, Ke; Xie, Lu; Peng, Ying; Fan, Jing; Kung, Hsiang-fu; Yao, Kai-Tai (1); Xu, Ren-He
CS (1) Department of Pathology, First Military Medical University, Guangzhou, 510515 China
SO Biochemical and Biophysical Research Communications, (***April 2, ***2000***) Vol 270, No 1, pp 293-297
ISSN 0006-291X

DT Article
LA English
SL English

AB Previously we have shown that blocking bone morphogenetic protein (BMP) receptor signaling by a dominant negative BMP receptor causes neurogenesis in *Xenopus* animal caps (ACs), whereas the physiological neural inducer noggin acts as a homodimer physically binding to ***BMP***-4 and ***disrupting*** its signaling at the ligand level. The present study attempted to elucidate the relationship between the structure and function of noggin. By replacing some cysteine residues with serine residues through a site-directed mutagenesis strategy, we generated three noggin mutants, C145S, C205S, and C(218, 220, 222)S (3CS). Although mRNAs encoded by these mutants were translated as efficiently as wild-type (WT) noggin mRNA, they behaved differently when expressed in vivo. Expression of WT noggin or C205S in *Xenopus* ACs converted the explants (prospective ectoderm) into neural tissue, indicated by the neural-like morphology and expression of the pan neural marker NCAM in the ACs. In contrast, ACs expressing C145S or 3CS sustained an epidermal fate like the control caps. Similar results were observed in the mesoderm where C205S (but not C145S and 3CS) displayed dorsalizing activity as well as WT noggin. Altogether, our results suggest that Cys145 alone or Cys(218, 220, 222) as a whole in noggin protein is required for the biological activities of noggin, probably participating in the dimerization of noggin with BMP-4 or itself.

L16 ANSWER 16 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2000 209359 BIOSIS
DN PREV200000209359

TI Dorsal and intermediate neuronal cell types of the spinal cord are established by a BMP signaling pathway
AU Nguyen, Vu H.; Trout, Jamie; Connors, Stephanie A.; Andermann, Peter; Weinberg, Eric; Mullins, Mary C. (1)
CS (1) Department of Cell and Developmental Biology, University of Pennsylvania School of Medicine, 421 Cune Blvd, 1211 BRBII/III, Philadelphia, PA, 19104-6058 USA
SO Development (Cambridge), (***March, 2000***) Vol 127, No 6, pp 1209-1220
ISSN: 0950-1991

DT Article

LA English

SL English

AB We have studied the role of Bmp signaling in patterning neural tissue through the use of mutants in the zebrafish that ***disrupt*** three different components of a ***Bmp*** signaling pathway: swirl/bmp2b, snailhouse/bmp7 and somitabun/smads5. We demonstrate that Bmp signaling is essential for the establishment of the prospective neural crest and dorsal sensory Rohon-Beard neurons of the spinal cord. Moreover, Bmp signaling is necessary to limit the number of intermediate-positioned lim1+ interneurons of the spinal cord, as observed by the dramatic expansion of these prospective interneurons in many mutant embryos. Our analysis also suggests a positive role for Bmp signaling in the specification of these interneurons, which is independent of Bmp2b/Swirl activity. We found that a presumptive ventral signal, Hh signaling, acts to restrict the amount of dorsal sensory neurons and trunk neural crest. This restriction appears to occur very early in neural tissue development, likely prior to notochord or floor plate formation. A similar early role for Bmp signaling is suggested in the specification of dorsal neural cell types, since the bmp2b/swirl and bmp7/snailhouse genes are only coexpressed during gastrulation and within the tail bud, and are not found in the dorsal neural tube or overlying epidermal ectoderm. Thus, a gastrula Bmp2b/Swirl and Bmp7/Snailhouse-dependent activity gradient may not only act in the specification of the embryonic dorsoventral axis, but may also function in establishing dorsal and intermediate neuronal cell types of the spinal cord.

L16 ANSWER 17 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2000 120971 BIOSIS

DN PREV200000120971

TI Oocyte-expressed TGF-beta superfamily members in female fertility

AU Elvin, Julia A.; Yan, Changning; Matzuk, Martin M. (1)

CS (1) Department of Pathology, Baylor College of Medicine, One Baylor Plaza, Houston, TX, 77030 USA

SO Molecular and Cellular Endocrinology, (***Jan 25, 2000***) Vol 159, No 1-2, pp 1-5
ISSN: 0303-7207

DT General Review

LA English

SL English

AB Folliculogenesis is regulated by the interplay of extraovarian and intraovarian factors, and the importance of each type of regulation varies depending on the developmental stage of the follicle. Preantral follicle development is regulated predominantly by factors produced locally within the ovary and within the follicle itself. The oocyte has been shown to produce soluble factor(s), which regulate a number of processes in follicular development, including cumulus expansion in the periovulatory period. Members of the TGFbeta superfamily are potent regulators of cell proliferation and differentiation in a number of organ systems, and three members, growth differentiation factor 9 (GDF-9), bone morphogenetic protein 15 (BMP-15) and BMP-6 are expressed by the oocyte and may mediate effects attributed to the oocyte. Based on ***knockout*** mouse models ***BMP***-6 does not play an essential role in ovarian function, but GDF-9 is absolutely required for preantral follicle development. GDF-9 also alters the periovulatory expression of granulosa cell genes and stimulates cumulus expansion. Although BMP-15 is expressed identically to GDF-9, its role in regulating ovarian function is still unknown. This review examines the similarities and differences in sequence, expression and function of the oocyte-expressed TGFbeta family members with respect to regulating folliculogenesis.

L16 ANSWER 18 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 1999 511137 BIOSIS

DN PREV199900511137

TI ***Transgenic*** over-expression of ***Bone***

Morphogenetic ***Protein***-7 in liver and kidney suggests a

role in maintaining normal renal and hepatocyte function in the adult

AU de Caestecker, Mark P. (1); Bassity, Corina M. (1); Nangle, Sarah; Factor, Valenbina M.; Roberts, Anita B. (1); Kopp, Jeffrey B.

CS (1) LCR, NCI, Bethesda, MD USA

SO Journal of the American Society of Nephrology, (***Sept, 1999***) Vol 10, No PROGRAM AND ABSTRACT ISSUE, pp 453A

Meeting Info: 32nd Annual Meeting of the American Society of Nephrology

Miami Beach, Florida, USA November 1-8, 1999 American Society of Nephrology

ISSN 1046-6673

DT Conference
LA English

L16 ANSWER 19 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC
AN 1999 455732 BIOSIS
DN PREV199900455732
TI Expression of bone morphogenetic protein-2 via adenoviral vector in C2C12 myoblasts induces differentiation into the osteoblast lineage
AU Okubo, Yasunori (1); Bessho, Kazuhisa; Fujimura, Kazuma; Iizuka, Tadahiko; Miyatake, Shin-ichi
CS (1) Department of Oral and Maxillofacial Surgery, Kyoto University, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, 606-8507 Japan
SO Biochemical and Biophysical Research Communications, (***Sept. 7,*** 1999***) Vol. 262, No. 3, pp 739-743
ISSN: 0006-291X

DT Article
LA English
SL English

AB To examine the effectiveness of a gene transfer of bone morphogenetic protein (BMP)-2 into C2C12 myoblasts, we constructed a human ***BMP***-2-expressing replication-***deficient*** adenoviral vector. Ax(CAO)BMP-2 C2C12 cells were infected in vitro with either this viral vector or an *Escherichia coli* LacZ gene-expressing control adenovirus vector. An efficient gene transfer to the C2C12 cells was confirmed with the LacZ gene-expressing vector by X-gal staining. Abundant BMP-2 expression in C2C12 cells infected with this viral vector was confirmed by immunofluorescence and Western blot analysis. C2C12 cells transferred with the BMP-2 gene by this vector produced alkaline phosphatase in the cells and also produced and secreted osteocalcin in the culture medium, demonstrating that a gene transfer of BMP-2 into C2C12 cells in vitro could convert these cells from myoblast to osteoblast lineage.

L16 ANSWER 20 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC
AN 1999 373758 BIOSIS
DN PREV199900373758
TI Collagen integrin receptors regulate early osteoblast differentiation induced by BMP-2
AU Jikko, Akitoshi; Harris, Stephen E.; Chen, Di; Mendenick, Donna L.; Damsky, Caroline H. (1)
CS (1) HSW 604, University of California-San Francisco, 513 Parnassus Avenue, San Francisco, CA 94143-0512 USA
SO Journal of Bone and Mineral Research, (***July, 1999***) Vol. 14, No. 7, pp 1075-1083
ISSN: 0884-0431.

DT Article
LA English
SL English

AB Studies in several cell types indicate that the actions of integrin receptors for extracellular matrix and receptors for growth factors are synergistic in regulating cellular differentiation and function. We studied the roles of the alpha1beta1 and alpha2beta1 integrin collagen receptors in regulating the differentiation of 2T3 osteoblastic cells in response to bone morphogenetic protein (BMP)-2. The immortalized 2T3 cell line was established from the calvaria of mice ***transgenic*** for a ***BMP***-2 promoter driving SV40 T-antigen. These cells require exogenous BMP-2, as well as ascorbic acid and beta-glycerophosphate, for expression of a mature osteoblast phenotype and formation of a mineralized matrix. To determine how integrin receptors for collagen-I affect BMP-2 signaling, function-perturbing anti-type I alpha1 and/or alpha2 integrin subunit, or anti-type I collagen (Col-I), antibodies were added to human recombinant (hr)BMP-2-treated 2T3 cultures at confluence (C0) or at 4 or 8 days postconfluence (C4, C8). After 4 days of exposure to the antibodies, cultures were assayed for alkaline phosphatase (ALP) mRNA levels and enzyme activity and for cAMP production in response to parathyroid hormone. Addition of anti-collagen-I or both anti-integrin-alpha1 and -alpha2 antibodies to C0 cultures blocked expression of these early osteoblast markers by more than 90%, and also blocked mineralization (0-5.1% control) of these cells. In all cases, adding anti-alpha1 or anti-alpha2 antibodies separately produced partial effects, while their combined effect approached that of anti-collagen-I. When antibodies were added to more differentiated 2T3 cells, the inhibitory effects decreased. 2T3 cells carrying constitutive type active BMP receptor (caBMPR-IB) showed elevated ALP activity without hrBMP-2, this constitutive activity was also suppressed by alpha1 and alpha2 integrin antibodies and by anti-Col-I antibody. Together, our data suggest that a signal(s) from collagen integrin receptors regulates the response to BMP downstream of BMPR-IB and upstream of the regulation of ALP mRNA and other early markers of osteoblast differentiation.

=> d his

(FILE 'HOME' ENTERED AT 11 05 42 ON 13 MAR 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11 06 21 ON 13 MAR 2003
L1 13855 S BONE MORPHOGENETIC PROTEIN? OR BMP
L2 11378 S BONE MORPHOGENETIC PROTEIN?
L3 1377 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DEL
L4 1139 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT?)

L5 871 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN?)
L6 501 S L1 AND (KNOCKOUT OR TRANSGEN?)
L7 258 S L1 (5A) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DE
L8 137 DUP REM L7 (121 DUPLICATES REMOVED)
L9 1625 S BMP-4
L10 174 S L9 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR DE
L11 86 DUP REM L10 (88 DUPLICATES REMOVED)
L12 203 S L8 OR L11
L13 28 S L9 (5A) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR DISRUPT? OR D
L14 13 DUP REM L13 (15 DUPLICATES REMOVED)
L15 126 S L8 NOT L14
L16 73 S L8 AND PY<=2000

=> d bib abs 21-40

L16 ANSWER 21 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC
AN 1999 249880 BIOSIS
DN PREV199900249880
TI Smad5 knockout mice die at mid-gestation due to multiple embryonic and extraembryonic defects
AU Chang, Hua; Huylenbroeck, Danny; Verschueren, Kristin; Guo, Quxia; Matzuk, Martin M. (1); Zwijsen, An
CS (1) Department of Pathology, Baylor College of Medicine, Houston, TX, 77030 USA
SO Development (Cambridge), (***April, 1999***) Vol. 126, No. 8, pp. 1631-1642
ISSN: 0950-1991

DT Article
LA English
SL English

AB Smad5 has been implicated as a downstream signal mediator for several bone morphogenetic proteins (BMPs). To understand the *in vivo* function of Smad5, we generated mice deficient in Smad5 using embryonic stem (ES) cell technology. Homozygous mutant embryos die between E9.5 and E11.5, and display variable phenotypes. Morphological defects are first detected at E8.0 in the developing amnion, gut and heart (the latter defect being similar to ***BMP***-2 ***knockout*** mice). At later stages, mutant embryos fail to undergo proper turning, have craniofacial and neural tube abnormalities, and are edematous. In addition, several extraembryonic lesions are observed. After E9.0, the yolk sacs of the mutants contain red blood cells but lack a well-organized vasculature, which is reminiscent of BMP-4, TGF-beta1 and TGF-beta type II receptor knockout mice. In addition, the allantois of many Smad5 mutants is fused to the chorion, but is not well-elongated. A unique feature of the Smad5 mutant embryos is that ectopic vasculogenesis and hematopoiesis is observed in the amnion, likely due to mislocation of allantois tissue. Despite the expression of Smad5 from gastrulation onwards, and in contrast to knockouts of Smad2 and Smad4, Smad5 only becomes essential later in extraembryonic and embryonic development.

L16 ANSWER 22 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC
AN 1999 237484 BIOSIS
DN PREV199900237484
TI Extracellular matrix-associated bone morphogenetic proteins are essential for differentiation of murine osteoblastic cells in vitro
AU Suzawa, Miyuki; Takeuchi, Yasuhiro (1); Fukumoto, Seiji; Kato, Shigeaki; Ueno, Naoto; Miyazono, Kohei; Matsumoto, Toshio; Fujita, Toshiro
CS (1) Fourth Department of Internal Medicine, University of Tokyo School of Medicine, 3-28-6 Mejirodai, Bunkyo-ku, Tokyo, 112-8688 Japan
SO Endocrinology, (***May, 1999***) Vol. 140, No. 5, pp. 2125-2133
ISSN: 0013-7227

DT Article
LA English
SL English

AB Osteoblastic differentiation is an essential part of bone formation that compensates resorbed bone matrix to maintain its structural integrity. Cells in an osteoblast lineage develop differentiated phenotypes during a long-term culture *in vitro*. However, intrinsic mechanisms whereby these cells differentiate into mature osteoblasts are yet unclear. Bone morphogenetic proteins (BMPs) stimulate osteoblastic differentiation and bone formation. We demonstrate that mouse osteoblastic MC3T3-E1 cells constitutively expressed messenger RNAs (mRNAs) for BMP-2 and BMP-4 and accumulated BMPs in collagen-rich extracellular matrices. BMPs associated with the extracellular matrices were involved in the induction of osteoblastic differentiation of nonosteogenic mesenchymal cells as well as cells in the osteoblast lineage. MC3T3-E1 cells constitutively expressed type Ia and type II ***BMP*** receptors. When a kinase-***deficient*** type Ia ***BMP*** receptor was stably transfected to MC3T3-E1 cells to obliterate BMP-2/4 signaling, these cells not only failed to respond to exogenous BMP-2 but lost their capability of differentiation into osteoblasts that form mineralized nodules. These observations strongly suggest that endogenous BMP-2/4 accumulated in extracellular matrices are essential for the osteoblastic differentiation of cells in the osteoblast lineage. Therefore, the regulatory mechanism of BMP-2/4 actions in osteoblastic cells is a principal issue to be elucidated for better understanding of pathogenesis of bone losing diseases such as osteoporosis.

L16 ANSWER 23 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1999 188485 BIOSIS
DN PREV199900188485

TI BMP signaling plays a role in visceral endoderm differentiation and cavitation in the early mouse embryo

AU Coucounavis, Electra (1); Martin, Gail R.

CS (1) Department of Cell Biology and Neuroanatomy, Institute of Human Genetics, University of Minnesota School of Medicine, 321 Church Street SE, 4144 Jackson Hall, Minneapolis, MN, 55455 USA

SO Development (Cambridge). (***Feb., 1999**) Vol. 126, No. 3, pp 535-546
ISSN 0950-1991.

DT Article

LA English

AB At E4.0 the inner cell mass of the mouse blastocyst consists of a core of embryonic ectoderm cells surrounded by an outer layer of primitive (extraembryonic) endoderm, which subsequently gives rise to both visceral endoderm and parietal endoderm. Shortly after blastocyst implantation, the solid mass of ectoderm cells is converted by a process known as cavitation into a pseudostratified columnar epithelium surrounding a central cavity. We have previously used two cell lines, which form embryoid bodies that do (PSA1) or do not (S2) cavitate, as an *in vitro* model system for studying the mechanism of cavitation in the early embryo. We provided evidence that cavitation is the result of both programmed cell death and selective cell survival, and that the process depends on signals from visceral endoderm (Coucounavis, E. and Martin, G. R. (1995) *Cell* 83, 279-287). Here we show that Bmp2 and Bmp4 are expressed in PSA1 embryoid bodies and embryos at the stages when visceral endoderm differentiation and cavitation are occurring, and that blocking ***BMP*** signaling via expression of a ***transgene*** encoding a dominant negative mutant form of BMP receptor IB inhibits expression of the visceral endoderm marker, Hnf4, and prevents cavitation in PSA1 embryoid bodies. Furthermore, we show that addition of BMP protein to cultures of S2 embryoid bodies induces expression of Hnf4 and other visceral endoderm markers and also cavitation. Taken together, these data indicate that BMP signaling is both capable of promoting, and required for differentiation of, visceral endoderm and cavitation of embryoid bodies. Based on these and other data, we propose a model for the role of BMP signaling during peri-implantation stages of mouse embryo development.

L16 ANSWER 24 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1999 169677 BIOSIS
DN PREV199900169677

TI ***BMP*** -5 ***deficiency*** alters chondrocytic activity in the mouse proximal tibial growth plate

AU Ballon-Plaza, A.; Lee, A. O.; Veson, E. C.; Farnum, C. E.; Van Der Meulen, M. C. H. (1)

CS (1) Sibley Sch. Mechanical Aerospace Eng., Cornell Univ., 222 Upson Hall, Ithaca, NY 14853-7501 USA

SO Bone (New York). (***March, 1999**) Vol. 24, No. 3, pp. 211-216
ISSN: 8756-3282

DT Article

LA English

AB The role of bone morphogenetic protein-5 (BMP-5) in regulating chondrocytic activity during endochondral ossification was examined in the mouse proximal tibial growth plate. Short ear mice homozygous for the SEA/Gn point mutation in the coding region for BMP-5 (King, J. A. et al. *Dev Biol* 166: 112-122, 1994) and heterozygous long ear littermates were examined at 5 and 9 weeks of age (n = 9/group, four groups). Animals were injected with oxytetracycline to estimate the rate of growth and with bromodeoxyuridine to identify proliferative chondrocytes. Age-related changes in chondrocytic stereological and kinetic parameters were compared by image analysis of 1-mum-thick growth plate sections. The number of proliferative chondrocytes did not vary with age in either genotype, but proliferative phase duration increased significantly (apprx67%) with age in the long ear mice, whereas no change was detected in the short ear mice. The number of hypertrophic chondrocytes increased significantly (apprx27%) in the short ears, whereas this number decreased significantly (apprx40%) in the long ears. There was a small, but significant, increase in hypertrophic phase duration (apprx45%) in short ear mice, but no change was detected in the long ears. These results indicate that ***BMP*** -5 ***deficiency*** prevents age-related decelerations in chondrocytic proliferation and initiation of hypertrophic differentiation, suggesting a role of BMP-5 in inhibiting these processes.

L16 ANSWER 25 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1999 85586 BIOSIS
DN PREV19990085586

TI ***Transgenic*** overexpression of ***bone*** ***morphogenetic*** ***protein*** -4 leads to abnormal neurologic function

AU Gomes, W. A.; Orcutt, E.; Kelic, S.; Kessler, J. A.

CS Dep. Neurosci. Albert Einstein Coll. Med., Bronx, NY 10461 USA

SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 2001
Meeting Info: 28th Annual Meeting of the Society for Neuroscience, Part 2
Los Angeles, California, USA November 7-12, 1998 Society for Neuroscience
ISSN 0190-5295

DT Conference

LA English

L16 ANSWER 26 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1999 80345 BIOSIS

DN PREV199900080345

TI Ectopic ***BMP*** -2, -4, -7 ***disrupts*** chick telencephalic development through repression of Shh and Fgf8 gene expression and apoptosis

AU Okubo, Y.; Rubenstein, J. L. R.

CS Ireland Lab., UCSF, 401 Parnassus, San Francisco, CA 94143-0984 USA

SO Society for Neuroscience Abstracts, (1998) Vol. 24, No. 1-2, pp. 1532
Meeting Info: 28th Annual Meeting of the Society for Neuroscience, Part 2
Los Angeles, California, USA November 7-12, 1998
ISSN: 0190-5295

DT Conference

LA English

L16 ANSWER 27 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1999 66145 BIOSIS

DN PREV199900066145

TI Mitogen-activated protein kinase and neural specification in *Xenopus*

AU Uzgare, Aarti R.; Uzman, J.; Akif, El-Hodiri, Hethem M.; Sater, Amy K. (1)

CS (1) Dep. Biol., Univ. Houston, Houston, TX 77204-5513 USA

SO Proceedings of the National Academy of Sciences of the United States of America, (***Dec., 1998**) Vol. 95, No. 25, pp. 14833-14838
ISSN: 0027-8424

DT Article

LA English

AB We have investigated the activity and function of mitogen-activated protein kinase (MAPK) during neural specification in *Xenopus*. Ectodermal MAPK activity increased between late blastula and midgastrula stages. At midgastrula, MAPK activity in both newly induced neural ectoderm and ectoderm overexpressing the anterior neural inducer noggin was 5-fold higher than in uninduced ectoderm. Overexpression of MAPK phosphatase-1 (MKP-1) in ectoderm inhibited MAPK activity and prevented neurlectoderm-specific gene expression when the ectoderm was recombined with dorsal mesoderm or treated with fibroblast growth factor (FGF). Neurlectoderm-specific gene expression was observed, however, in ectoderm overexpressing both noggin and MKP-1. To evaluate the role of MAPK in posterior regionalization, ectodermal isolates were treated with increasing concentrations of FGF and assayed for MAPK activity and neurlectoderm-specific gene expression. Although induction of posterior neural ectoderm by FGF was accompanied by an elevation of MAPK activity, relative MAPK activity associated with posterior neural fate was no higher than that of ectoderm specified to adopt an anterior neural fate. Thus, increasingly posterior neural fates are not correlated with quantitative increases in MAPK activity. Because MAPK has been shown to down-regulate Smad1, MAPK may ***disrupt*** ***bone*** ***morphogenetic*** ***protein*** -4 (BMP4) signaling during neural specification. Our results suggest that MAPK plays an essential role in the establishment of neural fate in vivo.

L16 ANSWER 28 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1999 49164 BIOSIS

DN PREV199900049164

TI Induction of bone morphogenetic protein-6 in skin wounds. Delayed reepithelialization and scar formation in ***BMP*** -6 overexpressing ***transgenic*** mice

AU Kaiser, Sibylle; Schirmacher, Peter; Philipp, Armin; Protschka, Martina; Moll, Ingrid; Nicol, Karin; Blessing, Manfred (1)

CS (1) Boehringer Ingelheim Res. Group, SFB-311, I. Medical Dep., Johannes Gutenberg-Univ., D-55131 Mainz Germany

SO Journal of Investigative Dermatology, (***Dec., 1998**) Vol. 111, No. 6, pp. 1145-1152
ISSN: 0022-202X

DT Article

LA English

AB Growth factors of the transforming growth factor-beta superfamily are involved in cutaneous wound healing. In this study we analyze the expression of the bone morphogenetic protein-6 (BMP-6) gene, a transforming growth factor-beta related gene, in skin wounds. In normal mouse skin high levels of BMP-6 mRNA and protein are expressed by postmitotic keratinocytes of stratified epidermis until day 6 after birth. BMP-6 expression is strongly reduced in adult epidermis with diminished mitotic activity. After skin injury we found large induction of BMP-6-specific RNA and protein in keratinocytes at the wound edge and keratinocytes of the newly formed epithelium as well as fibroblast-shaped cells in the wound bed. BMP-6-specific RNA was induced within 24 h after injury, whereas significant upregulation of BMP-6 on the protein level was detected only 2-3 d after injury. Protein was confined to outermost suprabasal epidermal layers, whereas BMP-6-specific RNA was distributed throughout all epidermal layers including basal keratinocytes and the leading edge of the migrating keratinocytes. We also detected high levels of BMP-6 specific RNA and protein in chronic human wounds of different etiology. In contrast to the overall distribution pattern of BMP-6-specific RNA, the protein was not detected in keratinocytes directly bordering the wound. In order to test the influence of BMP-6 abundance on the progress of wound healing, we analyzed the wound response of ***transgenic*** mice overexpressing ***BMP*** -6 in the epidermis. In these mice, reepithelialization of skin wounds was significantly delayed, suggesting that strict spatial and temporal regulation of BMP-6 expression is necessary not only for formation but also for

reestablishment of a fully differentiated epidermis

L16 ANSWER 29 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS

INC

AN 1998 428520 BIOSIS

DN PREV199800428520

TI Structural and functional analysis of the BMP-4 promoter in early embryos of *Xenopus laevis*

AU Metz Annette, Knoechel, Sigrun, Euechler, Peter, Koester, Manfred, Knoechel Walter (1)

CS (1) Abteilung Biochem., Univ Ulm, Albert-Einstein-Allee 11, D-89081 Ulm Germany

SO Mechanisms of Development, (***June, 1998***) Vol. 74, No. 1-2, pp. 29-39

ISSN 0925-4773

DT Article

LA English

AB The *Xenopus laevis* BMP-4 gene shows an evolutionary conserved structure containing two coding exons and a leader exon. The transcripts which are detected after zygotic activation of the gene in ventral mesoderm of late blastula stage embryos do either contain the leader exon or begin within the first intron. Luciferase reporter/promoter studies revealed multiple elements being required for the activation and for the spatial control of transcription. These elements are located within the upstream region and within the second intron and they interact with a most proximal located basal promoter being indispensable for transcriptional activation. The auto-activatory capacity of BMP-4 is mediated by several enhancer elements being responsive not only to BMP-4 but also to BMP-2 signaling. BMP-2 might thus function as a natural activator of the BMP-4 gene in the early embryo. Since reporter activity obtained with distinct ***BMP*** -2/4 responsive promoter ***deletion*** mutants is simultaneously inhibited by the dominant negative BMP receptor as well as by chordin, we suggest that down-regulation of the BMP-4 gene by chordin results from an interference with the auto-regulatory loop at the level of protein/protein interactions

L16 ANSWER 30 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS

INC

AN 1998 315938 BIOSIS

DN PREV199800315938

TI A clonal chondrocyte cell line derived from ***BMP*** -2/T antigen-expressing ***transgenic*** mouse

AU Xu, Chi (1), Ji, Xiaohui; Harris, Marie A.; Mundy, Gregory R.; Harris, Stephen E.

CS (1) Div. Endocrinol. Metabolism, Dep. Med., Univ. Texas Health Sci. Cent. San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284 USA

SO In Vitro Cellular & Developmental Biology Animal, (***May, 1998***) Vol. 34, No. 5, pp 359-363

ISSN 1071-2690

DT Letter

LA English

L16 ANSWER 31 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS

INC

AN 1998 224665 BIOSIS

DN PREV199800224665

TI Bone morphogenetic protein-7 (osteogenic protein-1, OP-1) and tooth development

AU Helder, M. N., Karg, H., Bervoets, T. J. M., Vokicic, S.; Burger, E. H.; D'Souza, R. N.; Woltgens, J. H. M.; Karsenty, G.; Bronckers, A. L. J. J. (1)

CS (1) Dep. Oral Cell Biol., ACTA, Vrije Univ., van der Boechorststr. 7, 1081 BT Amsterdam Netherlands

SO Journal of Dental Research, (***April, 1998***) Vol. 77, No. 4, pp 545-554

ISSN 0022-0345

DT Article

LA English

AB Bone morphogenetic proteins (BMPs) form a family of growth factors originally isolated from extracellular bone matrix that are capable of inducing bone formation ectopically. We studied the expression, tissue localization, and function of BMP-7 (OP-1) during tooth development in rodents. Patterns of BMP-7 gene expression and peptide distribution indicated that BMP-7 was present in dental epithelium during the dental lamina, bud, and cap stages. During the bell stage, BMP-7 mRNA expression and protein distribution shifted from dental epithelium toward the dental mesenchyme. With advancing differentiation of odontoblasts, BMP-7 protein staining in the dental papilla became restricted to the layer of fully functional odontoblasts in the process of depositing (pre)dentin. Secretory-stage ameloblasts exhibited weak immunostaining for BMP-7. A restricted pattern of staining in ameloblasts became apparent in post-secretory stages of amelogenesis. Also, cells of the forming periodontal ligament were immunopositive. Histological analysis of tooth development in neonatal ***BMP*** -7- ***deficient*** mice did not reveal obvious changes compared with wild-type mice. We conclude that, in developing dental tissues, BMP-7 has distribution and expression patterns similar to those of other BMP members but is not an essential growth factor for tooth development, possibly because of functional redundancy with other BMP members or related growth factors

L16 ANSWER 32 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS

INC

AN 1998 208314 BIOSIS

DN PREV199800208314

TI *Xenopus Smad8* acts downstream of BMP-4 to modulate its activity during vertebrate embryonic patterning

AU Nakayama, Takuwa, Snyder, Mark A.; Grewal, Savraj S.; Tsuneizumi, Kazuhide; Tabata, Tetsuya; Christian, Jan L. (1)

CS (1) Dep. Cell Dev. Biol., L215, Oregon Health Sci. Univ. Sch. Med., 3181 SW Sam Jackson Park Rd., Portland, OR 97201-3098 USA

SO Development (Cambridge), (***March, 1998***) Vol. 125, No. 5, pp. 857-867

ISSN 0950-1991

DT Article

LA English

AB Bone morphogenetic proteins (BMPs) participate in the development of nearly all organs and tissues. BMP signaling is mediated by specific Smad proteins, Smad1 and/or Smad5, which undergo serine phosphorylation in response to BMP-receptor activation and are then translocated to the nucleus where they modulate transcription of target genes. We have identified a distantly related member of the *Xenopus* Smad family, Smad8, which lacks the C-terminal SSXS phosphorylation motif present in other Smads, and which appears to function in the BMP signaling pathway. During embryonic development, the spatial pattern of expression of Smad8 mirrors that of BMP-4. We show that an intact BMP signaling pathway is required for its expression. Overexpression of Smad8 in *Xenopus* embryos phenocopies the effect of blocking BMP4 signaling, leading to induction of a secondary axis on the ventral side of intact embryos and to direct neural induction in ectodermal explants. Furthermore, Smad8 can block BMP-4-mediated induction of ventral mesoderm-specific gene expression in ectodermal explants. Overexpression of Smad8 within dorsal cells, however, causes patterning defects that are distinct from those reported in ***BMP*** -4- ***deficient*** embryos, suggesting that Smad8 may interact with additional signaling pathways. Indeed, overexpression of Smad8 blocks expression of Xbra in whole animals, and partially blocks activin signaling in animal caps. In addition, Smad8 inhibits involution of mesodermal cells during gastrulation, a phenotype that is not observed following blockade of activin or BMPs in *Xenopus*. Together, these results are consistent with the hypothesis that Smad8 participates in a negative feedback loop in which BMP signaling induces the expression of Smad8, which then functions to negatively modulate the amplitude or duration of signaling downstream of BMPs and, possibly, downstream of other transforming growth factor-beta (TGF-beta) family ligands.

L16 ANSWER 33 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS

INC

AN 1996 573072 BIOSIS

DN PREV199799287753

TI Mice deficient for BMP2 are nonviable and have defects in amnion/chorion and cardiac development

AU Zhang, Hongbing (1), Bradley, Allan

CS (1) Cardiovasc. Res. Inst., Univ. Calif., San Francisco, Parnassus Ave., San Francisco, CA 94143 USA

SO Development (Cambridge), (1996) Vol. 122, No. 10, pp 2977-2986

ISSN 0950-1991

DT Article

LA English

AB To address the function of bone morphogenetic protein-2 (BMP2) in mammalian development, mice with a targeted deletion of the Bmp2 mature region were generated using embryonic stem cell technology. This mutation caused embryonic lethality when homozygous. Mutant embryos failed to close the proamniotic canal, which caused the malformation of the amnion/chorion. Bmp2-deficient embryos also exhibited a defect in cardiac development, manifested by the abnormal development of the heart in the extraembryonic cavity. These defects are consistent with the expression of Bmp2 in the extraembryonic mesoderm cells and promyocardium. Thus BMP2 is a critical factor for both extraembryonic and embryonic development

L16 ANSWER 34 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS

INC

AN 1996 521429 BIOSIS

DN PREV199699243785

TI Overexpression of bone morphogenetic protein-6 (***BMP*** -6) in the epidermis of ***transgenic*** mice. Inhibition or stimulation of proliferation depending on the pattern of transgene expression and formation of psoriatic lesions

AU Blessing, Manfred (1), Schimacher, Peter, Kaiser, Sibylle

CS (1) Boehringer Ingelheim Res. Group, SFB-311, I. Med. Dep., Johannes Gutenberg-Univ., Obere Zahlbacher Str. 63, D-55131 Mainz Germany

SO Journal of Cell Biology, (1996) Vol. 135, No. 1, pp 227-239

ISSN 0021-9525

DT Article

LA English

AB Bone morphogenetic protein-6 (BMP-6) belongs to the family of TGF-beta-related growth factors. In the developing epidermis, expression of BMP-6 coincides with the onset of stratification. Expression persists perinatally but declines after day 6 postpartum, although it can still be detected in adult skin by reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. We constitutively overexpressed BMP-6 in suprabasal layers of interfollicular epidermis in transgenic mice using a keratin 10 promoter. All mice expressing the transgene developed abnormalities in the skin, indicating an active transgene-derived factor. Depending on the pattern of transgene expression, the effects on proliferation and differentiation were completely opposite. Strong and uniform expression of the ***BMP*** -6 ***transgene*** resulted in severe repression of

cell proliferation in embryonic and perinatal epidermis but had marginal effects on differentiation. Weaker and patchy expression of the transgene evoked strong hyperproliferation and parakeratosis in adult epidermis and severe perturbations of the usual pattern of differentiation. These perturbations included changes in the expression of keratins and integrins. Together with an inflammatory infiltrate both in the dermis and in the epidermis, these aspects present all typical histological and biochemical hallmarks of a human skin disease: psoriasis.

L16 ANSWER 35 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1996 481889 BIOSIS

DN PREV199699197145

TI Analysis of limb patterning in ***BMP*** -7- ***deficient*** mice

AU Hofmann, Clementine (1), Luo, Guangbin, Balling, Rudi, Karsenty, Gerard
CS (1) Forschungszentrum Umwelt Gesundheit, Inst. Saeugertiergenetik,
Neuherberg, Ingolstaedter Landstr. 1, D-85758 Oberschleissheim-Munich
Germany

SO Developmental Genetics, (1996) Vol. 19, No. 1, pp 43-50
ISSN 0192-253X

DT Article

LA English

AB Bone morphogenetic proteins (BMPs) are polypeptide signaling molecules, belonging to the TGF-beta superfamily. They were originally identified by their ability to induce ectopic bone formation, but their expression patterns in embryos suggest multiple functions. ***BMP*** -7- ***deficient*** mice show among other mesodermal and skeletal patterning defects, polydactyly in the hindlimbs (Luo G, Hofmann C, Bronckers ALJJ, Sohocki M, Bradley A, Karsenty G (1995) Genes Dev 9:2808-2820, Dudley AT, Lyons KM, Robertson EJ (1995) Genes Dev 9:2795-2807). Here we report a more detailed analysis of the limb phenotype in ***BMP*** -7- ***deficient*** mice using *in situ* hybridization to monitor expression of molecules implicated in patterning processes of the developing vertebrate limb. In previous studies we showed that Sonic hedgehog (Shh) was expressed normally, but Hoxd-13 expression in limb mesenchyme was lower in BMP-7 mutant limbs. Here we show that Hoxd-11 expression domains are also contracted and decreased in intensity in mutant limbs, suggesting that 5' genes of the Hoxd cluster are coordinately downregulated, while another Bmp, Bmp-Z which can be activated by Shh, is similarly expressed. The mutant limb buds are broader than normal buds, and fibroblast growth factor Fgf-8 is expressed throughout the extended ridge. However, expression of the homeobox gene Msx-1, which has been shown to be involved in epithelial-mesenchymal interactions during limb development, was decreased in the mesenchyme of BMP-7 mutant limbs. Taken together, our data suggest that BMP-7 is involved in regulating proliferation and/or epithelial-mesenchymal interactions in the developing limb.

L16 ANSWER 36 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1996 360366 BIOSIS

DN PREV199699082722

TI Mechanical and geometric changes in the growing femora of ***BMP*** -5- ***deficient*** mice

AU Mikic, B. (1), Van Der Meulen, M. C. H., Kingsley, D. M., Carter, D. R.
CS (1) Rehabilitation Res. Development Cent., Dep. Veterans Affairs Med
Cent., 3801 Miranda Avenue/153, Palo Alto, CA 94304-1200 USA
SO Bone (New York), (1996) Vol. 18, No. 6, pp 601-607.
ISSN 8756-3282.

DT Article

LA English

AB We examined the growth-related changes in femoral geometry and torsional strength in ***BMP*** -5- ***deficient*** short-ea mice over a 22-week time interval ("long-term" changes). Four groups of female mice (n = 6 per group) were examined: short-ea animals and their heterozygous control littermates at 4 and 26 weeks of age. In agreement with findings previously observed in a mixed-gender group of adult mice (26 weeks), the femora of short-ea animals were significantly smaller in length and cross section at both ages. The magnitudes of the differences between genotypes were comparable at each age, indicating that the overall rates of appositional and endochondral growth were similar for both genotypes over the 22-week period. In the adult animals, short-ea femora were 27 +/- 7% weaker in torsional strength due to their smaller cross-sectional geometry. However, bone strength in adult short-ea mice appeared to be adequate for animal size. No significant difference was detected in maximum femoral torque when normalized by body mass. In 4-week old animals, ***BMP*** -5- ***deficiency*** was associated with a 27 +/- 6% lower body mass, but the torsional strength of the femur was not significantly different from that of controls. Cross-sectional geometry was smaller in 4-week old short-ea mice, but the apparent bone material ultimate shear stress was elevated by 33 +/- 10%, thereby resulting in a whole bone torsional strength equivalent to that of the larger control mice. While the data suggest a higher material strength in the 4-week-old short-ea animals, no significant difference in the level of bone mineralization was detectable between genotypes at either age.

L16 ANSWER 37 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1996 57503 BIOSIS

DN PREV199698629638

TI ***Disruption*** of ***BMP*** signals in embryonic Xenopus ectoderm leads to direct neural induction

AU Hawley, Stephanie H. B., Wunnenberg-Stapleton, Katrin, Hashimoto, Chikara, Laurent, Micheline N., Watabe, Tetsuro, Blumberg, Bruce W., Cho, Ken W. Y.

(1)
CS (1) Dev. Biology Cent., Dep. Dev. Cell Biology, Univ. Calif., Irvine, CA
92717-2300 USA

SO Genes & Development, (1995) Vol. 9, No. 23, pp 2923-2935
ISSN 0890-9369

DT Article

LA English

AB Bone morphogenetic proteins (BMPs), which have been implicated in the patterning of mesoderm, are members of the transforming growth factor-beta (TGF-beta) superfamily. We have investigated the roles of *Xenopus* BMP-7 (XBMP-7) and BMP-4 (XBMP-4), and activin (another TGF-beta-related molecule) in early development by generating dominant-negative versions of these growth factors. Mutations were generated by altering the cleavage sites that are required for maturation of the active dimeric forms of XBMP-7, XBMP-4, and activin. These mutant constructs, designated Cm-XBMP-7, Cm-XBMP-4, and Cm-activin, result in polypeptides that allow for dimerization of the subunits, but are incapable of maturation. Expression of Cm-XBMP-7 and Cm-XBMP-4, but not Cm-activin, in the ventral marginal zone of the *Xenopus* embryo results in the development of a secondary axis, similar to that seen by ectopic expression of the truncated BMP receptor. These results suggest that the cleavage mutants interfere with BMP signaling during mesodermal patterning. We also found that expression of Cm-XBMP-7 or Cm-XBMP-4 in animal cap ectoderm directly induces neuroectoderm. The neural induction was specific for Cm-XBMP-7 and Cm-XBMP-4 because ectopic expression of Cm-activin or Vg-1 did not mimic the same phenotype. Molecular study of neural patterning by Cm-XBMP-7 and Cm-XBMP-4 revealed that only anterior neuroectodermal markers are expressed in response to these Cm-XBMPs. These results suggest that the BMPs are involved in the specification of ectoderm in *Xenopus* development, and that neural induction requires the removal of BMP signals in the ectoderm. We propose that neural induction occurs by a default mechanism, whereby the inhibition of BMP signaling is required for the conversion of ectoderm to neuroectoderm in the developing *Xenopus* embryo.

L16 ANSWER 38 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1996 57484 BIOSIS

DN PREV199698629619

TI BMP-7 is an inducer of nephrogenesis and is also required for eye development and skeletal patterning

AU Luo, Guangbin, Hofmann, Clementine, Bronckers, Antonius L. J. J., Sohocki, Melanie, Bradley, Allan, Karsenty, Gerard
CS Dep. Oral Cell Biol., Acad. Cent. Dent. Amsterdam, Vrije Univ
Boechorstr., Amsterdam Netherlands

SO Genes & Development, (1995) Vol. 9, No. 22, pp. 2808-2820.
ISSN 0890-9369.

DT Article

LA English

AB Bone morphogenetic proteins (BMPs) are multifunctional growth factors originally identified by their ability to induce ectopic bone formation. To investigate the function of one of the BMPs, BMP-7, we have generated ***BMP*** -7- ***deficient*** mice using embryonic stem cell technology. ***BMP*** -7- ***deficient*** mice die shortly after birth because of poor kidney development. Histological analysis of mutant embryos at several stages of development revealed that metanephric mesenchymal cells fail to differentiate, resulting in a virtual absence of glomerulus in newborn kidneys. *In situ* hybridization analysis showed that the absence of BMP-7 affects the expression of molecular markers of nephrogenesis, such as Pax-2 and Wnt-4 between 12.5 and 14.5 days postcoitum (dpc). This identifies BMP-7 as an inducer of nephrogenesis. In addition, ***BMP*** -7- ***deficient*** mice have eye defects that appear to originate during lens induction. Finally, ***BMP*** -7- ***deficient*** mice also have skeletal patterning defects restricted to the rib cage, the skull, and the hindlimbs.

L16 ANSWER 39 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1996 57483 BIOSIS

DN PREV199698629618

TI A requirement for bone morphogenetic protein-7 during development of the mammalian kidney and eye

AU Dudley, Andrew T., Lyons, Karen M., Robertson, Elizabeth J. (1)
CS (1) Dep. Mol. Cell Biol., Harv. Univ., Cambridge, MA 02138 USA

SO Genes & Development, (1995) Vol. 9, No. 22, pp. 2795-2807.
ISSN: 0890-9369.

DT Article

LA English

AB BMP-7/OP-1, a member of the transforming growth factor-beta (TGF-beta) family of secreted growth factors, is expressed during mouse embryogenesis in a pattern suggesting potential roles in a variety of inductive tissue interactions. The present study demonstrates that mice lacking BMP-7 display severe defects confined to the developing kidney and eye. Surprisingly, the early inductive tissue interactions responsible for establishing both organs appear largely unaffected. However, the absence of ***BMP*** -7- ***disrupts*** the subsequent cellular interactions required for their continued growth and development. Consequently, homozygous mutant animals exhibit renal dysplasia and anophthalmia at birth. Overall, these findings identify BMP-7 as an essential signaling molecule during mammalian kidney and eye development.

L16 ANSWER 40 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1996 55918 BIOSIS

DN PREV199698628053

TI Immortalized murine osteoblasts derived from ***BMP*** 2-T-antigen expressing ***transgenic*** mice.
AU Ghosh-Choudhury, Nandini; Windle, Jolene J.; Koop, Barbara A.; Harris, Marie A.; Guerrero, Daniel L.; Wozney, John M.; Mundy, Gregory R.; Harris, Stephen E. (1)
CS (1) Dep. Medicine/Endocrinol., Univ. Tex. Health Sci. Cent., 7703 Floyd Curl Drive, San Antonio, TX 78284-7877 USA
SO Endocrinology, (1996) Vol 137, No. 1, pp 331-339
ISSN 0013-7227

DT Article

LA English

AB Osteoblast cell lines capable of undergoing bone formation in vitro would provide useful models for understanding gene expression during bone cell differentiation. To that end, transgenic mice were produced using a 2.9-kilobase bone morphogenetic protein 2 (BMP-2) promoter fragment, driving simian virus 40 T antigen as the transgene. The expression of simian virus 40 T antigen driven by the BMP-2 promoter immortalizes the cells. From the calvaria of the transgenic mouse, several osteoblastic cell lines were isolated and cloned. One clonal osteoblast cell line, called 2T3, has been characterized and shown to produce mineralized bone nodules. Recombinant human BMP-2 (rhBMP-2) accelerates the formation of these mineralized bone nodules. 2T3 cells express alkaline phosphatase, collagen type I, osteocalcin, and endogenous BMP-2 messenger RNA (mRNA)

in

a similar chronological order as normal freshly isolated fetal rat calvarial cells during early nodule formation and subsequent mineralization. The 2T3 cells also exhibit extensive growth and multilayering during differentiation, as demonstrated by growth curves and transmission electron microscopy. As with freshly isolated fetal rat calvarial cells, 1,25-dihydroxyvitamin D₃ inhibited alkaline phosphatase activity and alkaline phosphatase mRNA expression, but stimulated osteocalcin mRNA expression. rhBMP-2 also accelerated the expression of alkaline phosphatase activity and mRNA, osteocalcin mRNA, and BMP-2 mRNA in 2T3 cells along with the formation of larger and more mineralized bone nodules. The 2T3 cell exhibits autoregulation of endogenous BMP-2 by rhBMP-2 ligand. This is shown at the mRNA and transcriptional levels. The 2T3 osteoblast cell line offers a system for examining autoregulation of the BMP-2 gene and downstream gene expression during osteoblast differentiation. 2T3 cells are reclonable and maintain their differentiation capabilities.

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YOU HAVE REQUESTED DATA FROM 33 ANSWERS - CONTINUE? Y/(N): y

L16 ANSWER 41 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1996 18206 BIOSIS

DN PREV199698590341

TI Bone morphogenetic protein acts as a ventral mesoderm modifier in early *Xenopus* embryos

AU Suzuki, Atsushi; Shioda, Noriko; Ueno, Naoto (1)

CS (1) Fac. Pharmaceutical Sciences, Hokkaido Univ., Sapporo 060 Japan

SO Development Growth & Differentiation, (1995) Vol. 37, No. 5, pp 581-588
ISSN 0012-1592.

DT Article

LA English

AB Mesoderm of early vertebrate embryos gradually acquires dorsal-ventral polarity during embryogenesis. This specification of mesoderm is thought to be regulated by several polypeptide growth factors. Bone morphogenetic protein (BMP), a member of the TGF-beta 8 family, is one of the regulators suggested to be involved in the formation of ventral mesoderm. In this paper, the nature of the endogenous BMP signal in dorsal-ventral specification was assessed in early *Xenopus* embryos using a dominant negative mutant of the *Xenopus* ***BMP*** receptor. In ectodermal explant assays, ***disruption*** of endogenous ***BMP*** signaling by the mutant receptor changed the competence of the explant cells to mesoderm-inducing factors, activin and basic fibroblast growth factor (bFGF), and led to formation of neural tissue without mesoderm induction. This result suggests that endogenous BMP acts as a ventral mesoderm modifier rather than a ventral mesoderm inducer, and that interactions between endogenous BMP and mesoderm-inducing factors may be important in dorsal-ventral patterning of embryonic mesoderm. In addition, the induction of neural tissue by inhibition of the BMP signaling pathway also suggests involvement of BMP in neural induction.

L16 ANSWER 42 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1995 479916 BIOSIS

DN PREV199598494216

TI Long bone geometry and strength in adult ***BMP*** -5 ***deficient*** mice

AU Mikic, B (1); Van Der Meulen, M. C. H.; Kingsley, D. M.; Carter, D. R.
CS (1) Rehabilitation Res. Dev. Cent., Dep. Veterans Affairs Med. Cent., 3801
Miranda Avenue 153, Palo Alto, CA 94304-1200 USA

SO Bone (New York), (1995) Vol. 16, No. 4, pp 445-454
ISSN 8756-3282

DT Article

LA English

AB Bone morphogenetic proteins (BMPs) play a critical role in early skeletal development. BMPs are also potential mediators of bone response to mechanical loading, but their role in later stages of bone growth and

adaptation has yet to be studied. We characterized the postcranial skeletal defects in mature mice with ***BMP*** ***deficiency*** by measuring hind-limb muscle mass and long bone geometric, material, and torsional mechanical properties. The animals studied were 26-week-old short ear mice (n = 10) with a homozygous ***deletion*** of the ***BMP*** -5 gene and their heterozygous control litter mates (n = 15).

Gender-related effects, which were found to be independent of genotype, were also examined. The femora of short ear mice were 3% shorter than in controls and had significantly lower values of many cross-sectional geometric and structural strength parameters (p < 0.05). No significant differences in ash content or material properties were detected. Lower femoral whole bone torsional strength was due to the smaller cross-sectional geometry (16% smaller section modulus) in the short ear mice. The diminished cross-sectional geometry may be commensurate with lower levels of in vivo loading, as reflected by body mass (-8%) and quadriceps mass (-11%). While no significant gender differences were found in whole bone strength or cross-sectional geometry, males had significantly greater body mass (+18%) and quadriceps mass (+15%) and lower tibio-fibular ash content (-3%). The data suggest that adult female mice have a more robust skeleton than males, relative to in vivo mechanical demands. Furthermore, although the bones of short ear mice are smaller and weaker than in control animals, they appear to be biomechanically appropriate for the in vivo mechanical loads that they experience.

L16 ANSWER 43 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1995 255921 BIOSIS

DN PREV199598270221

TI Chemical skin carcinogenesis is prevented in mice by the induced expression of a TGF-beta related transgene

AU Blessing, Manfred (1); Nanney, Lillian B.; King, Lloyd E.; Hogan, Brigid L. M.

CS (1) Med. Klinik, Poliklinik, Johannes Gutenberg Univ., Mainz Germany

SO Teratogenesis Carcinogenesis and Mutagenesis, (1995) Vol. 15, No. 1, pp 11-21.
ISSN 0270-3211.

DT Article

LA English

AB Skin papillomas and squamous cell carcinomas (SCCs) are induced in mice by

tumor initiation with a carcinogen followed by tumor promotion with the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA). These usually arise from preneoplastic lesions characterized by epidermal proliferation and hyperplasia, dermal edema, and inflammation. To evaluate the role of polypeptide growth factors in chemically induced skin carcinogenesis, we used transgenic mice carrying the cDNA for a TGF-beta related molecule, bone morphogenetic protein-4 (BMP-4), under the control of the regulatory elements of the cytokeratin IV* gene in a skin carcinogenesis protocol. Control non- ***transgenic*** littermates and ***BMP*** -4 ***transgenic*** mice were treated with a single dose of a carcinogen, N-methyl-N-nitrosoguanidine (MNNG), and biweekly with the tumor promoter TPA for 9 months. In control littermates TPA induced epidermal hyperproliferation, atypia with "dark" cells, and dermal inflammation, resulting in papillomas and SCCs in 13 of 26 animals tested. In ***BMP*** -4 ***transgenic*** mice, TPA treatment induced the expression of the ***BMP*** -4 ***transgene*** in interfollicular epidermis but only minimal epidermal thickening, hyperproliferation, and inflammation were noted after the initial dose of TPA. Furthermore, the mitotic indices in transgenic epidermis after 9 months of TPA treatment were significantly lower than the corresponding indices from untreated transgenic epidermis. Consequently, none of the 22 transgenic animals tested developed papillomas or SCCs. In conclusion, we have shown that the TPA induced expression of the ***BMP*** -4 ***transgene*** blocks proliferation and inflammation in skin, steps that are critical to the subsequent formation of papillomas and SCCs and we characterized an inducible promotersystem which expresses polypeptides in interfollicular epidermis after exogenous stimulation.

L16 ANSWER 44 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1994 383735 BIOSIS

DN PREV199497396735

TI ***Deletion*** of the ***BMP*** -5 gene in mice results in altered adult long bone morphology.

AU Mikic, B (1); Van Der Meulen, M. C. H.; Kingsley, D. M.; Carter, D. R.

CS (1) Stanford Univ., Stanford, CA USA

SO Journal of Morphology, (1994) Vol. 220, No. 3, pp 372
Meeting Info: Fourth International Congress of Vertebrate Morphology

Chicago, Illinois, USA July 31-August 4, 1994

ISSN 0362-2525

DT Conference

LA English

L16 ANSWER 45 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC

AN 1993 229420 BIOSIS

DN PREV199395120595

TI Transgenic mice as a model to study the role of TGF-beta-related molecules in hair follicles

AU Blessing, Manfred (1); Nanney, Lillian B.; King, Lloyd E.; Jones, C.

Michael, Hogan, Brigid L. M.

CS (1) Dep. Cell Biol., Vanderbilt Univ. Sch. Med., Nashville, TN 37232 USA

SO Genes & Development, (1993) Vol 7, No 2, pp 204-215
 ISSN 0890-9369
 DT Article
 LA English
 AB There is increasing evidence that members of the TGF-beta superfamily are important regulators of epithelial growth and differentiation *in vivo*. Here, transgenic mice have been used to study the role of the TGF-beta-related growth factors BMP-2 and BMP-4 in hair and whisker development. In the mature hair follicle, 3MP-2 transcripts are normally seen only in preconter cells at the base of the hair shaft. In the ***transgenic*** mice reported here, ***BMP***-4, a closely related molecule, has been ectopically expressed in the outer root sheath of hair and whisker follicles using an expression vector based on the bovine cytokeratin IV promoter. In response to transgene expression, both outer root sheath cells below the stem cell compartment and hair matrix cells around the dermal papilla cease proliferation. In addition, the expression pattern of cytokeratin markers is disturbed in some transgenic hair follicles. These results support a model in which members of the TGF-beta superfamily play an active role in the inhibition of cell proliferation and the onset of expression of trichocyte-specific genes that take place when cells leave the matrix of the follicle and differentiate into shaft cells.

L16 ANSWER 46 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS
 INC
 AN 1993 73879 BIOSIS
 DN PREV199395038379
 T The mouse short ear skeletal morphogenesis locus is associated with defects in a bone morphogenetic member of the TGF-beta superfamily
 AU Kirsley, David M. (1), Bland, Adrienne E. (1), Grubbs, Janet M., Marker, Pau C. (1), Russell, Liane B., Copeland, Neal G., Jenkins, Nancy A.
 CS (1: Dep. Developmental Biol., Beckman Center B300, Stanford Univ. Sch. Med., Stanford, Calif. 94305-5427
 SO Cell, (1992) Vol. 71, No. 3, pp 399-410.
 ISSN 0092-8674
 DT Article
 LA English
 AB The mouse short ear gene is required for normal growth and patterning of skeletal structures, and for repair of bone fractures in adults. We have carried out an extensive chromosome walk in the chromosome region that surrounds this locus. Here we show that the short ear region contains the gene for a TGF-beta-related protein called bone morphogenetic protein 5 (***Bmp**-5). This gene is ***deleted*** or rearranged in several independent mutations at the short ear locus. Mice homozygous for large ***deletions*** of the ***Bmp**-5 coding region are viable and fertile. Mutations at the short ear locus provide an important new tool for defining the normal functions of BMPs in mammals. The specific skeletal defects seen in short-eared animals, which occur against a background of otherwise normal skeletal structures, suggest that particular aspects of skeletal morphology may be determined by individual members of a family of signaling factors that can induce the formation of cartilage and bone *in vivo*.

L16 ANSWER 47 OF 73 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS
 INC
 AN 1992 222422 BIOSIS
 DN BR42 103922
 TI HYPERACTIVITY INDUCED BY A SNAP-25 INCLUSIVE DELETION MUTATION IN COLOBOMA
 CM-POSITIVE MOUSE MUTANTS
 AU HESS E J, JINNAH H A, WILSON M C
 CS DEP. NEUROPHARM., RES INST SCRIPPS CLIN., LA JOLLA, CALIF 92037, USA
 SO 21ST ANNUAL MEETING OF THE SOCIETY FOR NEUROSCIENCE, NEW ORLEANS,
 LOUISIANA, USA, NOVEMBER 10-15, 1991 SOC NEUROSCI ABSTR (1991) 17 (1-2): 892
 CODEN ASNEES
 DT Conference
 FS BR OLD
 LA English

L16 ANSWER 48 OF 73 EMBASE COPYRIGHT 2003 ELSEVIER SCI B.V.
 AN 1999055664 EMBASE
 TI A clonal chondrocytic cell line derived from ***BMP***-2/T antigen-expressing ***transgenic*** mouse [3]
 AU Xu C., Ji X., Harris M.A., Mundy G.R., Harris S.E.
 CS C. Xu, Div. of Endocrinology and Metabolism, Department of Medicine, Univ. of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284, United States
 SO In Vitro Cellular and Developmental Biology - Animal, (1998) 34/5 (359-363).
 ISSN 1071-2690 CODEN: ICDBEO
 CY United States
 DT Journal, Letter
 FS 021 Developmental Biology and Teratology
 LA English

L16 ANSWER 49 OF 73 EMBASE COPYRIGHT 2003 ELSEVIER SCI B.V.
 AN 1998032480 EMBASE
 TI Animal models of heterotopic ossification
 AU O'Connor J.P.

CS Dr J P O'Connor, Department of Orthopaedics, Univ Med /Dent Sch of New Jersey, New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103, United States
 SO Clinical Orthopaedics and Related Research, (1998) /-346 (71-80)
 Refs 85
 ISSN 0009-921X CODEN CORTBR
 CY United States
 DT Journal, Conference Article
 FS 005 General Pathology and Pathological Anatomy
 033 Orthopedic Surgery
 LA English
 SL English
 AB Heterotopic ossification is often a severe clinical complication of joint arthroplasty, neurologic trauma, and muscle injury. In rare genetic disorders such as fibrodysplasia ossificans progressiva, heterotopic ossification can be crippling and often leads to premature death. Reliable animal models of heterotopic ossifications that mimic pathologies seen in man would be invaluable for the development of new treatments to combat heterotopic ossification. Various methods used to induce heterotopic ossification in animals including the use of bone morphogenetic proteins, urinary tract epithelia, and transformed cell lines are described. Genetic animal models of heterotopic ossification and various miscellaneous examples of heterotopic ossification in animals are described. Finally, the use of ***transgenic*** mice to manipulate ***bone*** ***morphogenetic*** ***protein*** expression is discussed as a possible future animal model of heterotopic ossification.

L16 ANSWER 50 OF 73 EMBASE COPYRIGHT 2003 ELSEVIER SCI B.V.
 AN 96279912 EMBASE
 DN 1996279912
 TI BMP 7 is required for nephrogenesis, eye development, and skeletal patterning
 AU Karsenty G., Lu G., Hofmann C., Bradley A.
 CS Department of Molecular Genetics, Univ. Texas MD Anderson Cancer Ctr., Houston, TX 77030, United States
 SO Annals of the New York Academy of Sciences, (1996) 785/- (98-107).
 ISSN 0077-8923 CODEN ANYAA
 CY United States
 DT Journal, Conference Article
 FS 301 Anatomy, Anthropology, Embryology and Histology
 021 Developmental Biology and Teratology
 022 Human Genetics
 029 Clinical Biochemistry
 LA English
 SL English
 AB In summary, the generation of ***BMP***-7- ***deficient*** mice has provided additional evidence that this family of growth factors regulate many morphogenetic processes including but not limited to skeletal development. In particular our experiments demonstrate that BMP 7 acts as an early inducer of glomeruli formation, and that it is required for skeletal patterning and lens formation. Our results not only demonstrate that BMP 7 is involved in the differentiation of several organs during development, but also raise the hypothesis that mutations in the Bmp 7 gene itself or in the genetic pathway could be responsible for several human genetic diseases in which glomerulus formation is impaired.

L16 ANSWER 51 OF 73 EMBASE COPYRIGHT 2003 ELSEVIER SCI B.V.
 AN 94378774 EMBASE
 DN 1994378774
 TI Expression of the BMP 2 gene during bone cell differentiation
 AU Ghosh-Choudhury N., Harris M.A., Feng J.Q., Mundy G.R., Harris S.E.
 CS Division of Endocrinology/Metabolism, Department of Medicine, Texas University Health Science Ctr., San Antonio, TX 78284-7877, United States
 SO Critical Reviews in Eukaryotic Gene Expression, (1994) 4/2-3 (345-355).
 ISSN 1045-4403 CODEN CRGEEJ
 CY United States
 DT Journal, Article
 FS 021 Developmental Biology and Teratology
 022 Human Genetics
 029 Clinical Biochemistry
 LA English
 SL English
 AB Bone morphogenetic protein 2 (BMP 2) and transforming growth factor beta (TGF beta) are actively involved in bone formation and remodeling. TGF beta, a powerful stimulant in the early stage of bone cell growth and matrix formation, inhibits differentiation and *in vitro* mineralized nodule formation in primary fetal rat calvarial osteoblast system. TGF beta also negatively regulates BMP 2 expression at the transcriptional level. BMP 2 gene expression is controlled by a battery of transcriptional factors, some known and some yet to be identified. Immortalized osteoblast cell lines generated from a ***transgenic*** mouse carrying ***BMP***-2 promoter-driven SV40 large T antigen transgene are described as powerful tools for studying regulation of BMP 2 gene expression and bone cell differentiation at the molecular level.

L16 ANSWER 52 OF 73 EMBASE COPYRIGHT 2003 ELSEVIER SCI B.V.
 AN 94331598 EMBASE
 DN 1994331598
 TI Bone and cartilage differentiation
 AU Reddi A.H.
 CS Department of Orthopaedic Surgery, Johns Hopkins Univ School Medicine, Ross Research Building 225, 720 Rutland Avenue, Baltimore, MD 21205-2196.

United States

SO Current Opinion in Genetics and Development, (1994) 4/5 (737-744)

ISSN 0959-437X CODEN COGDET

CY United Kingdom

DT Journal, General Review

FS 021 Developmental Biology and Teratology

LA English

SL English

AB Recent progress in the study of regulation of bone and cartilage

differentiation has come from the isolation, cloning, and expression of genes encoding bone morphogenetic proteins (BMPs). BMPs initiate cartilage and bone formation in a sequential cascade. Their pleiotropic effects on chemotaxis, mitosis, and differentiation are based on concentration-dependent thresholds. The existence of multiple members of the BMP family raises issues concerning functional redundancy. Current work in progress in different laboratories has revealed that ***BMP*** -2 or ***BMP*** -4 gene ***knockout*** by homologous recombination results, surprisingly, in embryonic lethality. Cartilage and bone differentiation during endochondral development involves a continuum of steps: initiation, promotion, maintenance, modeling, and termination. The signaling factors for initiation and maintenance are being defined at the molecular level, and future studies will focus on the gene regulation of initial signaling molecules such as BMPs. Critical progress in the determination of the role of BMPs in bone development has been accomplished by systematic study of skeletal mutations such as short ear and brachyopidism in mice. The accelerating pace of advance in this area augurs well for the resolution of the molecular basis of morphogenesis of bone and cartilage.

L16 ANSWER 53 OF 73 CAPLUS COPYRIGHT 2003 ACS

AN 2000 828139 CAPLUS

DN 134 126420

TI Transgenically ectopic expression of Bmp4 to the Msx1 mutant dental mesenchyme restores downstream gene expression but represses Shh and Bmp2

in the enamel knot of wild type tooth germ

AU Zhao, X.; Zhang, Z.; Song, Y.; Zhang, X.; Zhang, Y.; Hu, Y.; Fromm, S. H.; Chen, Y.

CS Department of Cell and Molecular Biology and Center for Bioenvironmental Research, Tulane University, New Orleans, LA, 70118, USA

SO Mechanisms of Development (***2000***), 99(1,2), 29-38

CODEN MEDVE6, ISSN 0925-4773

PB Elsevier Science Ireland Ltd.

DT Journal

LA English

AB Bmp4 is a downstream gene of Msx1 in early mouse tooth development. In this study, we introduced the Msx1-Bmp4 transgenic allele to the Msx1 mutants in which tooth development is arrested at the bud stage in an effort of rescuing Msx1 mutant tooth phenotype in vivo. Ectopic expression of a Bmp4 transgene driven by the mouse Msx1 promoter in the dental mesenchyme restored the expression of Lef-1 and Dlx2 but neither Fgf8 nor syndecan-1 in the Msx1 mutant molar tooth germ. The mutant phenotype of molar but not incisor could be partially rescued to progress to the cap stage. The Msx1-Bmp4 transgene was also able to rescue the alveolar processes and the neonatal lethality of the Msx1 mutants. In contrast, overexpression of Bmp4 in the wild type molar mesenchyme down-regulated Shh and Bmp2 expression in the enamel knot, the putative signaling center for tooth patterning, but did not produce a tooth phenotype. These results indicate that Bmp4 can bypass Msx1 function to partially rescue molar tooth development in vivo, and to support alveolar process formation. Expression of Shh and Bmp2 in the enamel knot may not represent crit. signals for tooth patterning.

RE CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 54 OF 73 CAPLUS COPYRIGHT 2003 ACS

AN 2000 722346 CAPLUS

DN 133 331276

TI Bone morphogenetic protein-1 processes probiglycan

AU Scott, Ian C.; Imamura, Yasutada; Pappano, William N.; Troedel, James M.; Recklies, Anneliese D.; Roughley, Peter J.; Greenspan, Daniel S.

CS Department of Pathology and Laboratory Medicine, University of Wisconsin, Madison, WI, 53706, USA

SO Journal of Biological Chemistry (***2000***), 275(39), 30504-30511

CODEN JBCHA3, ISSN 0021-9258

PB American Society for Biochemistry and Molecular Biology

DT Journal

LA English

AB Bone morphogenetic protein-1 (BMP-1) is a metallo-protease that plays important roles in regulating the deposition of fibrous extracellular matrix in vertebrates, including provision of the procollagen C-proteinase activity that processes the major fibrillar collagens I-III. Biglycan, a small leucine-rich proteoglycan, is a nonfibrillar extracellular matrix component with functions that include the pos. regulation of bone formation. Biglycan is synthesized as a precursor with an NH2-terminal propeptide that is cleaved to yield the mature form found in vertebrate tissues. Here, we show that BMP-1 cleaves biglycan at a single site, removing the propeptide and producing a biglycan mol. with an NH2 terminus identical to that of the mature form found in tissues. BMP-1-related proteases mammalian Tolloid and mammalian Tolloid-like 1 (mTLL-1) are shown to have low but detectable levels of biglycan-cleaving activity. Comparison shows that wild type mouse embryo fibroblasts (MEFs) produce only fully processed biglycan, whereas MEFs derived from embryos

homozygous null for the Bmp1 gene, which encodes both BMP-1 and

mammalian

Tolloid, produce predominantly unprocessed probiglycan, and MEFs homozygous null for both the Bmp1 gene and the mTLL-1 gene Tll1 produce only unprocessed probiglycan. Thus, all detectable probiglycan-processing activity in MEFs is accounted for by the products of these two genes.

RE CNT 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 55 OF 73 CAPLUS COPYRIGHT 2003 ACS

AN 2000 715097 CAPLUS

DN 134 37456

TI BMP-induced ectopic bone formation in osteopetrotic (op/op) mice

AU Yamasaki, Akira; Sakurai, Yuuko; Sugiura, Junko; Watanabe, Shun; Ito, Hiroshi; Oida, Shinichiro

CS Department of Oral Pathology, Ohu University School of Dentistry, Fukushima, 963-8611, Japan

SO Journal of Hard Tissue Biology (***2000***), 9(1), 1-6

CODEN JHTBF, ISSN 1341-7649

PB Society of Hard Tissue Biology

DT Journal

LA English

AB Osteopetrotic (op/op) mice suffer from a severe deficiency of monocytes/macrophages and osteoclasts due to a genetic derangement in M-CSF prodn. In this study, the authors examd. the process of ectopic bone formation by implantation of recombinant human BMP-2 (rhBMP-2)/Insol. rat bone collagen complex into mice in a macrophage/osteoclast-deficient condition. The rhBMP was produced by use of a baculovirus-insect cell (Sf-9) system. In both op/op mice and their phenotypically normal littermates, not only endochondral but also intramembranous bone was induced 1 wk after implantation. At 2 wk after implantation, the ectopic bone in normal littermates mostly consisted of mature bone with a sign of remodeling. In contrast, the ectopic bone in op/op mice appeared to exhibit the morphol. characteristics of woven bone and calcified cartilage as was obsd. at 1 wk, and retained this configuration unchanged at 11 wk. The authors thus conclude that the deficiency of monocytes/macrophages and osteoclasts does not affect the induction of bone/cartilage but results in the failure of the maturation of ectopic bone.

RE CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 56 OF 73 CAPLUS COPYRIGHT 2003 ACS

AN 2000 458103 CAPLUS

DN 133 191518

TI Cellular and molecular mechanism of low-turnover osteopenia in the klotho-deficient mouse

AU Kawaguchi, H.; Manabe, N.; Chikuda, H.; Nakamura, K.; Kuro-O, M.

CS Department of Orthopaedic Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, 113-8655, Japan

SO Cellular and Molecular Life Sciences (***2000***), 57(5), 731-737

CODEN: CMLSF, ISSN: 1420-682X

PB Birkhaeuser Verlag

DT Journal

LA English

AB The mouse homozygous for a disruption of the klotho locus (KL-/- or klotho mouse) exhibited multiple pathol. conditons resembling human aging. We obsd. osteopenia in KL-/- mice with a low bone turnover, in which the decrease in bone formation exceeded the decrease in bone resorption and resulted in net bone loss. This pathophysiol. resembles closely that of senile osteoporosis in humans. Osteoblastic cells from KL-/- mice proliferated normally in vitro, however, they showed much lower alk. phosphatase activity and mineralized matrix formation than those from control mice. Cultured osteoclastic cells from KL-/- mice had normal resorbing activity and survival rate, but the differentiation of osteoclastic cells from their precursors was significantly disturbed: in the co-culture of osteoblastic cells and osteoclast precursor cells, the formation of tartrate-resistant acid phosphatase-pos. multinucleated osteoclastic cells was extremely poor only when osteoclast precursor cells originated from KL-/- mice independently of the origin of the osteoblastic cells. In addn., we found that osteoprotegerin a secreted factor which inhibits osteoclastogenesis, was up-regulated in KL-/- mice. We conclude that a defect in klotho gene expression leads to the independent impairment of osteoblast and osteoclast differentiation, which can be a cause of low-turnover osteoporosis.

RE CNT 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 57 OF 73 CAPLUS COPYRIGHT 2003 ACS

AN 2000 375316 CAPLUS

DN 133 359312

TI Functions of BMP signaling molecules in development of mice

AU Beppu, Hideyuki

CS Cardiovasc. Res. Cent., Massachusetts General Hosp.-East, Harvard Med Sch., 149 13th Street, Charlestown, MA, 02129, USA

SO Molecular Medicine (Tokyo) (***2000***), 37(6), 648-653

CODEN: MOLMEL, ISSN: 0918-6557

PB Nakayama Shoten

DT Journal, General Review

LA Japanese
 AB A review with 20 refs. on recent findings obtained by using ***knockout*** mice about functional roles of ***BMP*** signaling mols. and BMP receptors in ontogeny and early development of mice

L16 ANSWER 58 OF 73 CAPLUS COPYRIGHT 2003 ACS
 AN 2000 375295 CAPLUS
 DN 133 318611
 TI BMP signal and chondrogenesis
 AU Iwamoto, Motomi
 CS Fac Dent, Osaka Univ, Japan
 SO Osaka Daigaku Shigaku Zasshi (***2000***), 44(2), 104-112
 CODEN ODSZA2 ISSN 0473-4629
 PB Osaka Daigaku Shigaku
 DT Journal, General Review
 LA Japanese
 AB A review with 37 refs. on expressions of BMP (bone morphogenetic proteins) and BMP receptors in cartilage, on effects of BMP on chondrocyte differentiation and cartilage formation, on roles of BMP in formation and differentiation of cartilage studied by ***BMP*** receptor gene mutations and ***transgenic*** mice

L16 ANSWER 59 OF 73 CAPLUS COPYRIGHT 2003 ACS
 AN 2000 8994 CAPLUS
 DN 132 31286
 TI Recombinant preparation of human ***bone*** ***morphogenetic*** ***protein*** -3 with ***transgenic*** Escherichia coli using plasmid vector containing double cistrons
 IN Chen, Sumin, Liu, Xinpeng, Bo, Qin, Lu, Zifan, Chen, Nanchun
 PA Fourth Medical University, PLA, Peop Rep China
 SO Farming Zhuanli Shengqing Gongkai Shuomingshu, 6 pp
 CODEN CNXXEV
 DT Patent
 LA Chinese
 FAN CNT 1
 PATENT NO. KIND DATE APPLICATION NO. DATE
 PI CN 1165189 A 19971119 CN 1996-118679 19960510 <..
 PRAI CN 1996-118679 19960510
 AB Described is a method for the prepn. of human bone morphogenetic protein-3 (hBMP-3), by using plasmid vectors pEC and pGC that contain era (E. coli ras-like protein gene) and gft (glutathione transferase gene), resp., as their 1st cistron and the gene for hBMP-3 as the 2nd cistron. The purified hBMP-3 possesses effective bone inducing activity in animals

L16 ANSWER 60 OF 73 CAPLUS COPYRIGHT 2003 ACS
 AN 1999 537942 CAPLUS
 DN 131 154461
 TI Transformation in situ of bone progenitor cells in the treatment of bone damage and disease
 IN Bonadio, Jeffrey, Goldstein, Steven A.
 PA The Regent of the University of Michigan, USA
 SO U. S. 72 pp, Cont.-in-part of U. S. 5,763,416
 CODEN: USXXAM
 DT Patent
 LA English
 FAN CNT 5
 PATENT NO. KIND DATE APPLICATION NO. DATE
 PI US 5942496 A 19990824 US 1994-318650 19940930 <..
 US 5763416 A 19980609 US 1994-199780 19940218 <..
 CA 2183542 AA 19950824 CA 1995-2183542 19950221 <..
 WO 9522611 A2 19950824 WO 1995-US2251 19950221 <..
 WO 9522611 A3 19960208
 W, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UG
 RV, KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG
 AU 9519686 A1 19950904 AU 1995-19686 19950221 <..
 AU 698936 B2 19981112
 EP 741785 A1 19961113 EP 1995-912589 19950221 <..
 EP 741785 B1 19991103
 P, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
 JP C0590825 T2 19971007 JP 1995-520840 19950221 <..
 JP 3354634 B2 20000819
 AT 186327 E 19991115 AT 1995-912589 19950221 <..
 ES 2139889 T3 20000216 ES 1995-912589 19950221 <..
 US 6074840 A 20000613 US 1995-479722 19950607 <..
 US 5962427 A 19991005 US 1996-631334 19960412 <..
 US 2002193338 A1 20021219 US 2002-177680 20020620
 PRAI US 1994-199780 A2 19940218
 US 1994-316650 A 19940930
 WO 1995-US2251 W 19950221
 US 1999-344581 B1 19990625
 AB Methods of transforming bone progenitor cells to stimulate growth and promote bone growth, repair and regeneration in vivo are described. Implants based on type II collagen are particularly effective in stimulating cell growth and transformation and genes involved in bone growth, development, and repair are used. Gene transfer protocols are disclosed for use in transferring various nucleic acid materials into

bone, as may be used in treating various bone-related diseases and defects including fractures, osteoporosis, osteogenesis imperfecta and in connection with bone implants. Fibrous type II collagen soaked in DNA was used to introduce DNA carrying reporter genes into bone at an osteotomy site. The use of an adenovirus vector to introduce a parathyroid hormone gene into an osteotomy site with successful expression of the gene and stimulated bone repair in a rat model. The cloning of a gene for a novel protein of the microfibrils is reported. The protein is fibrillin-like, but is smaller than a typical fibrillin and shows similarity to transforming growth factor beta-binding proteins. The gene was widely expressed in the developing fetus

RE CNT 339 THERE ARE 339 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 61 OF 73 CAPLUS COPYRIGHT 2003 ACS
 AN 1999 382509 CAPLUS
 DN 131 156098
 TI Targeted disruption of the homeobox transcription factor Nkx2-3 in mice results in postnatal lethality and abnormal development of small intestine and spleen
 AU Pabst, Oliver, Zweigerdt, Robert, Arnold, Hans-Henning
 CS Department of Cell and Molecular Biology, University of Braunschweig, Braunschweig, 38106, Germany
 SO Development (Cambridge, United Kingdom) (***1999***), 126(10), 2215-2225
 CODEN DEVDPB, ISSN 0950-1991
 PB Company of Biologists Ltd
 DT Journal
 LA English
 AB The homeodomain transcription factor Nkx2-3 is expressed in gut mesenchyme and spleen of embryonic and adult mice. Targeted inactivation of the Nkx2-3 gene results in severe morphol. alterations of both organs and early postnatal lethality in the majority of homozygous mutants. Villus formation in the small intestine appears considerably delayed in Nkx2-3/- fetuses due to reduced proliferation of the epithelium, while massively increased growth of crypt cells ensues in surviving adult mutants. Interestingly, differentiated cell types of the intestinal epithelium are present in homozygous mutants, suggesting that Nkx2-3 is not required for their cell lineage allocation or migration-dependent differentiation. Hyperproliferation of the gut epithelium in adult mutants is assocd. with markedly reduced expression of BMP-2 and BMP-4, suggesting that these signaling mols. may be involved in mediating non-cell-autonomous control of intestinal cell growth. Spleens of Nkx2-3 mutants are generally smaller and contain drastically reduced nos. of lymphatic cells. The white pulp appears anatomically disorganized, possibly owing to a homing defect in the spleen parenchyma. Moreover, some of the Nkx2-3 mutants exhibit asplenia. Apparently, Nkx2-3 is essential for normal development and functions of the small intestine and spleen

RE CNT 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 62 OF 73 CAPLUS COPYRIGHT 2003 ACS
 AN 1999 71907 CAPLUS
 DN 130 178305
 TI New method for screening bone formation-promoting agents using transgenic animal cells expressing PEBP2 alpha
 IN Harada, Hideyuki, Tagashira, Akizou, Fujiwara, Shouhan, Katsumata, Takashi, Nakatsuka, Masashi
 PA Sumitomo Pharmaceuticals Co., Ltd., Japan
 SO Jpn Kokai Tokkyo Koho, 11 pp
 CODEN: JKXXAF
 DT Patent
 LA Japanese
 FAN CNT 1
 PATENT NO. KIND DATE APPLICATION NO. DATE
 PI JP 11018787 A2 19990126 JP 1998-129650 19980422 <..
 PRAI JP 1997-121735 19970423
 AB Described is a method for screening bone formation-promoting agents by using mesenchyme cells or pre-fat cells transformed with the cDNA for PEBP2 alpha. Induction of differentiation into osteoblasts can be monitored by colorimetry of alk. phosphatase, which can be further increased by the presence of BMP (bone morphogenetic protein). Co-transformation of mouse C3H10T1/2 cells with a plasmid encoding PEBP2 alpha A and a plasmid encoding ***BMP***, induction of the ***transgenic*** C3H10T1/2 cells with all-trans retinoic acid, and observation of the expression of alk. phosphatase were shown. Use of pre-fat cells MC3T3-G2/PA6 for the screening is also claimed. The method is useful for screening therapeutics for osteoporosis

L16 ANSWER 63 OF 73 CAPLUS COPYRIGHT 2003 ACS
 AN 1998 728033 CAPLUS
 DN 130 93699
 TI Deficient expression of mRNA for the putative inductive factor bone morphogenetic protein-7 in chemically initiated rat nephroblastomas
 AU Higinbotham, Kathleen G., Karanava, Irina D., Diwan, Bhalchandra A., Peranton, Alan O.
 CS Laboratory of Comparative Carcinogenesis, Frederick Cancer Research and Development Center, National Cancer Institute, Frederick, MD, 21702, USA
 SO Molecular Carcinogenesis (***1998***), 23(2), 53-61

CODEN MOCAE8, ISSN 0899-1987

PB Wiley-Liss, Inc
DT Journal
LA English
AB Wilms' tumor, or nephroblastoma, arises from metanephric blastema and caricatures renal organogenesis. An alteration in at least one of the genes involved in control of renal differentiation is therefore a likely event in tumorigenesis, and indeed some of the genes involved in renal development, for example, hepatocyte growth factor (HGF) and its receptor c-met, the transcription factor Wilms' tumor gene (WT1), and transforming growth factor- β family member bone morphogenetic protein (BMP)-7, have also been implicated in various models of tumorigenesis. In a comparison of mRNA expression patterns for these genes in normal rat embryo/fetal kidney and nephroblastoma, we found that the patterns for HGF, met, and WT1 detected by *in situ* hybridization or RNase protection assay (RPA) in the nephroblastomas were similar to those of normal developing kidney. BMP-7 expression, on the other hand, was lower in most tumors examined, both by *in situ* hybridization and RPA than in normal tissues. This deficiency in a defined inductive factor that has been shown to function in renal tubulogenesis may play a role in tumorigenesis by allowing the accumulation of blastemal populations typical of nephroblastomas.

RE.CNT 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 64 OF 73 CAPLUS COPYRIGHT 2003 ACS
AN 1998 261034 CAPLUS

DN 129 2908

TI Inhibition of NF- κ B activity results in disruption of the apical ectodermal ridge and aberrant limb morphogenesis

AU Bushdid, Paul B.; Brantley, Dana M.; Yull, Fiona E.; Blaeuer, Gareth L.; Hoffman, Loren H.; Niswander, Lee; Kerr, Lawrence D.

CS Dep. Microbiol. Immunol., Vanderbilt Univ. Sch. Med., Nashville, TN, 37232-2363, USA

SO Nature (London) (***1998***), 392(6676), 615-618

CODEN: NATUAS, ISSN 0028-0836

PB Macmillan Magazines

DT Journal

LA English

AB In *Drosophila*, the Dorsal protein establishes the embryonic dorso-ventral axis during development. The vertebrate homolog of Dorsal, nuclear factor- κ B (NF- κ B), is vital for the formation of the proximo-distal organizer of the developing limb bud, the apical ectodermal ridge (AER). Transcription of the NF- κ B proto-oncogene c-rel is regulated, in part, during morphogenesis of the limb bud by AER-derived signals such as fibroblast growth factors. Interruption of NF- κ B activity using viral-mediated delivery of an inhibitor results in a highly dysmorphic AER, redn. in overall limb size, loss of distal elements and reversal in the direction of limb outgrowth. Furthermore, inhibition of NF- κ B activity in limb mesenchyme leads to a redn. in expression of Sonic hedgehog and Twist but derepresses expression of the bone morphogenetic protein-4 gene. These results are the first evidence that vertebrate NF- κ B proteins act to transmit growth factor signals between the ectoderm and the underlying mesenchyme during embryonic limb formation.

RE.CNT 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L16 ANSWER 65 OF 73 CAPLUS COPYRIGHT 2003 ACS
AN 1997 302265 CAPLUS

DN 126 316199

TI Enhancement of ectopic bone formation in mice with a deficit in Fas-mediated apoptosis

AU Mori, Shiro; Nose, Masato; Chiba, Masatoshi; Narita, Kenji; Kumagai, Masahiro; Kosaka, Hiromi; Teshima, Teiichi

CS Second Department of Oral and Maxillofacial Surgery, Tohoku University School of Dentistry, Sendai, 980-77, Japan

SO Pathology International (***1997***), 47(2/3), 112-116

CODEN: PITEES, ISSN: 1320-5463

PB Blackwell

DT Journal

LA English

AB Bone formation is under the control of cytokines as well as growth factors such as bone morphogenetic proteins (BMP). This suggests the possibility that osteogenesis might be modulated by factors which also modulate the immune system. To test whether immune disorders in the host may influence bone formation, the authors studied BMP-induced bone formation in a C3H/HeJ strain of mice bearing a mutant gene, the lymphoproliferative gene (lpr) or the generalized lymphoproliferative disease gene (gld), both of which are known to be a Fas deletion mutant and a Fas ligand mutant, resp., and to induce immune disorders via a deficit in Fas-mediated apoptosis. Crude BMP derived from bovine bone were injected into the muscular tissue in the femur of adult C3H/HeJ mice or C3H/HeJ mice bearing an lpr or gld gene. Quant. anal. of the resulting ectopic bone formation by x-ray photog. 2 wk after injection revealed that the presence of either the lpr or gld gene caused a bone mass significantly larger in dimension than that seen in the wild type mice. Histol. examn. also revealed the different influence between these mutant genes on the level of bone formation exhibited by hyaline cartilage and bone trabeculae. Based on these results, the authors discussed the possible mechanisms of the enhanced ectopic bone formation under the deficit in Fas-mediated

apoptosis

L16 ANSWER 66 OF 73 CAPLUS COPYRIGHT 2003 ACS

AN 1995 856269 CAPLUS

DN 123 248549

TI Preparation of transgenic animals secreting heterologous proteins into mammary gland using the mC26 gene expression system

IN Sato, Hiroyasu; Takao, Makoto

PA Sumitomo Metal Ind., Japan

SO Jpn. Kokai Tokkyo Koho, 34 pp

CODEN: JKXXAF

DT Patent

LA Japanese

FAN CNT 1

PATENT NO KIND DATE APPLICATION NO DATE

PI JP 07194380 A2 19950801 JP 1993-355132 19931228 <-

PRAI JP 1993-355132 19931228

AB Gene mC26, a gene codes for a protein highly expressed in the lactating mouse mammary gland, has been isolated and its enhancer/promoter region characterized. The regulatory region of the gene mC26 can be used for the prepn. of an expression cassette for producing heterologous proteins into the mammary gland of transgenic animals. Plasmid pBmC26EH encoding a fusion protein of human and hamster bone-morphogenetic proteins was prep'd and used for prep'g transgenic mice

L16 ANSWER 67 OF 73 CAPLUS COPYRIGHT 2003 ACS

AN 1995 822321 CAPLUS

DN 123 277162

TI Gene cloning and expression of mature peptide of bone morphogenetic protein-1 in Escherichia coli

AU Zhao, Ming; Lu, Li; Wang, Huixin; Zhou, Tingchong

CS Institute of Basic Medical Sciences, Academy of Military Medical Sciences, Beijing 100850, Peop. Rep. China

SO Gaojishu Tongxun (***1995***), 5(4), 41-5

CODEN: GTONE8, ISSN: 1002-0470

PB Gaojishu Tongxun Zazhishie

DT Journal

LA Chinese

AB Bone morphogenetic protein-1 (BMP-1) plays an important role in the bone formation and interactions with other BMPs. In this research, ***BMP***-1 cDNA was modified by ***deleting*** most of C terminus, leader sequence and nontranslation region, and the gene coding mature peptide of N terminus of BMP-1 was cloned by polymerase chain reaction. The initiation codon ATG and termination codon TGA were added to 5' and 3' termini of 1.3 kb coding gene resp., which was identified by DNA sequencing. In construction of expression plasmid of BMP-1, the E. coli vector, pBV-220, was used. The sequenced coding gene was inserted into MCS of pBV-220 under the control of the promoter PRP_L. After temp. induction, E. coli contg. pBV-BMP-1 plasmid expressed recombinant product in an inclusion body. SDS-PAGE showed that the mol. wt. of the recombinant mature peptide of BMP-1 was about 52 KDa, which was demonstrated by Western blot

L16 ANSWER 68 OF 73 CAPLUS COPYRIGHT 2003 ACS

AN 1994 526010 CAPLUS

DN 121 126010

TI Recombinant Vgr-1/BMP-6-expressing tumors induce fibrosis and endochondral bone formation in vivo

AU Gitelman, Stephen E.; Kobrin, Michael S.; Ye, Jian-Qin; Lopez, Alfredo R.; Lee, Angela; Deryckx, Rik

CS VA Med. Cent., Univ. California, San Francisco, CA, 94143, USA

SO Journal of Cell Biology (***1994***), 126(6), 1595-609

CODEN: JCLBA3, ISSN: 0021-9525

DT Journal

LA English

AB Members of the TGF- β superfamily appear to modulate mesenchymal differentiation, including the processes of cartilage and bone formation. Nothing is yet known about the function of the TGF- β -related factor vgr-1, also called bone morphogenetic protein-6 (BMP-6), and only limited studies have been conducted on the most closely related factors BMP-5, osteogenic protein-1 (OP-1) or BMP-7, and OP-2. Because vgr-1 mRNA has been localized in hypertrophic cartilage, this factor may play a vital role in endochondral bone formation. Antibodies were developed to vgr-1, and vgr-1 protein was confirmed to be expressed in hypertrophic cartilage of mice. To further characterize the role of this protein in bone differentiation, CHO cells were generated that overexpressed recombinant murine vgr-1 protein. Western blot anal. documented that recombinant vgr-1 protein was secreted into the media and was proteolytically processed to yield the mature vgr-1 mol. To assess the biol. activity of recombinant vgr-1 in vivo, vgr-1-expressing CHO cells were introduced directly into the s.c. tissue of athymic nude mice. CHO-vgr-1 cells produced localized tumors, and the continuous secretion of vgr-1 resulted in tumors with a strikingly different gross and histol. appearance as compared to the parental CHO cells. The tumors of control CHO cells were hemorrhagic, necrotic, and friable, whereas the CHO-vgr-1 tumors were dense, firm, and fibrotic. In contrast with control CHO tumors, the nests of CHO-vgr-1 tumor cells were surrounded by extensive connective tissue, which contained large regions of cartilage and bone. Further anal. indicated that secretion of vgr-1 from the transfected CHO tumor cells induced the surrounding host mesenchymal cells to develop along the endochondral bone pathway. These findings suggest that endogenous vgr-1

acts as an osteoinductive factor during endochondral bone formation.					
L16 ANSWER 69 OF 73 CAPLUS COPYRIGHT 2003 ACS					
AN 1994 317326 CAPLUS					
DN 120 317326					
TI Peptide and protein fusions to thioredoxin and thioredoxin-like molecules					
IN McCoy, John, Lavallie, Edward R					
PA Genetics Institute, Inc., USA					
SO PCT Int Appl., 43 pp					
CODEN PIXXD2					
DT Patent					
LA English					
FAN CNT 5					
PATENT NO. KIND DATE APPLICATION NO. DATE					
PI WO 9402502 A1 19940203 WO 1993-US6913 19930723 <..					
W AU, CA, JP					
RW AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
US 5292646 A 19940308 US 1992-921848 19920728 <..					
AU 9347814 A1 19940214 AU 1993-47814 19930723 <..					
PRAI US 1992-921848 A 19920728					
US 1991-652531 B2 19910206					
US 1991-745382 A2 19910814					
WO 1993-US6913 W 19930723					
AB A fusion mol comprising a DNA sequence encoding a thioredoxin-like protein and a DNA sequence encoding a selected heterologous peptide or protein is disclosed for the prodn of high levels of stable and sol. fusion protein. The peptide or protein may be used to the amino terminus of the thioredoxin-like mol, the carboxyl terminus of the thioredoxin-like mol, or within the thioredoxin-like mol, for example at the active-site loop of said mol. The fusion protein, located in the bacterial cytoplasm, may be selectively released from the cell by osmotic shock or freeze/thaw procedures. Prepn of the fusion of thioredoxin with human macrophage inflammatory protein 1 alpha or other proteins was demonstrated. It may be optionally cleaved to liberate the sol, correctly folded heterologous protein from the thioredoxin-like portion					
L16 ANSWER 70 OF 73 CAPLUS COPYRIGHT 2003 ACS					
AN 1993 464927 CAPLUS					
DN 119 64927					
TI Recombinant ***bone*** ***morphogenetic*** ***protein*** heterodimers and their manufacture with ***transgenic*** cells					
IN Israel, David; Wolfman, Neil M					
PA Genetics Institute, Inc., USA					
SO PCT Int Appl., 198 pp					
CODEN PIXXD2					
DT Patent					
LA English					
FAN CNT 2					
PATENT NO. KIND DATE APPLICATION NO. DATE					
PI WO 9309229 A1 19930513 WO 1992-US59430 19921102 <..					
W AU, BR, CA, FI, HU, JP, KR, NO, RU					
RW AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE					
AU 9230622 A1 19930607 AU 1992-30622 19921102 <..					
AU 674500 B2 19970102					
EP 612348 A1 19940831 EP 1992-924237 19921102 <..					
R AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, SE					
US 5866364 A 19990202 US 1992-989847 19921127 <..					
US 6190880 B1 20010220 US 1995-469411 19950606					
PRAI US 1991-787496 A 19911104					
US 1992-864692 A 19920407					
WO 1992-US59430 A 19921102					
US 1992-989847 A1 19921127					
AB A method for producing heterodimeric ***bone*** ***morphogenetic*** ***proteins*** (BMPs) comprises culturing a ***transgenic*** cell expressing 2 different ***BMP*** genes and isolating the heterodimeric BMP from the medium. CHO cells cotransfected with plasmids encoding BMP-2 or BMP-4 and with plasmids encoding BMP-5, BMP-6, or BMP-7 produced heterodimeric BMPs. These heterodimers stimulated W20 cells to produce more alk. phosphatase activity than did the individual BMP homodimers or mixts of homodimers. The heterodimers also preformed better in an in vivo test, the rat ectopic bone formation assays					
L16 ANSWER 71 OF 73 CAPLUS COPYRIGHT 2003 ACS					
AN 1993 464926 CAPLUS					
DN 119 64926					
TI DNA sequences encoding BMP-6 proteins and their expression in transgenic cells					
IN Wozney, John M; Wang, Elizabeth A; Rosen, Vicki A					
PA Genetics Institute, Inc., USA					
SO U.S. 24 pp. Cont.-in-part of U.S. Ser. No. 370,544.					
CODEN USXXAM					
DT Patent					
LA English					
FAN CNT 8					
PATENT NO. KIND DATE APPL CATION NO. DATE					
PI US 5187076 A 19930216 US 1990-490033 19900307 <..					
US 4877864 A 19891031 US 1987-31346 19870326 <..					
ZA 8704681 A 19880427 ZA 1987-4681 19870629 <..					
EP 688869 A1 19951227 EP 1995-111771 19870630 <..					
R AT, BE, CH, DE, FR, GB, IT, LU, NL, SE					
EP 1254956 A2 20021106 EP 2002-14841 19870630					
EP 1254956 A3 20021113					
R AT, BE, CH, DE, FR, GB, IT, LU, NL, SE					
US 5013649 A 19910507 US 1988-179100 19880408 <..					
CA 2030518 AA 19900929 CA 1990-2030518 19900327 <..					
WO 9011366 A1 19901004 WO 1990-US1630 19900327 <..					
W AU, CA, JP, KR					
RW AT, BE, CH, DK, ES, FR, GB, IT, LU, NL, SE					
AU 9053577 A1 19901022 AU 1990-53577 19900327 <..					
AU 624940 B2 19920625					
EP 429570 A1 19910605 EP 1990-905830 19900327 <..					
EP 429570 B1 19980114					
R AT, BE, CH, DE, DK, ES, FR, GB, IT, LU, NL, SE					
AT 162223 E 19980115 AT 1990-905830 19900327 <..					
ES 2113857 T3 19980516 ES 1990-905830 19900327 <..					
US 5108922 A 19920428 US 1990-561496 19900731 <..					
US 632919 B1 20020813 US 1991-655578 19910334					
US 5366875 A 19941122 US 1991-764731 19910924 <..					
US 5459047 A 19951017 US 1994-251069 19940527 <..					
US 5849880 A 19981215 US 1995-469936 19950606 <..					
JP 10070989 A2 19980317 JP 1997-171615 19970627 <..					
JP 3093682 B2 2001003					
US 6207813 B1 20010327 US 1998-189157 19981109					
US 2002061577 A1 20020523 US 2001-816299 20010323					
PRAI US 1988 880776 B2 19860701					
US 1986-943332 B2 19861217					
US 1987-28285 B2 19870320					
US 1987-31346 A2 19870326					
US 1988-179100 A2 19880408					
US 1988-179101 B2 19880408					
US 1988-179197 A2 19880408					
US 1989-329610 B2 19890328					
US 1989-347559 B2 19890504					
US 1989-370544 A2 19890623					
EP 1987-905023 A3 19870630					
EP 1995-111771 A3 19870630					
JP 1993-130389 A3 19870630					
US 1989-370547 A 19890623					
US 1989-370549 A 19890623					
US 1989-437409 A 19891115					
US 1989-438919 A 19891117					
US 1990-490033 A 19900307					
WO 1990-US1630 A 19900327					
US 1992-926081 A3 19920805					
US 1994-251063 A1 19940527					
US 1995-469936 A1 19950606					
US 1998-189157 A3 19981109					
AB cDNA encoding human and bovine bone morphogenic protein 6 (BMP-6), a vector contg said cDNA, a host cell expressing the BMP-6 cDNA, and a method for prepng BMP-6 with the transformed cell are claimed. The bovine BMP-6 was purified and partially sequenced, and oligonucleotide probes based on this sequence used to isolated a cDNA encoding a BMP-6 C-terminal fragment. This cDNA was used to screen a human placenta cDNA library for a full-length BMP-6 clone					
L16 ANSWER 72 OF 73 CAPLUS COPYRIGHT 2003 ACS					
AN 1993 464006 CAPLUS					
DN 119 64006					
TI Mouse bone morphogenic protein (BMP) cDNA cloning and expression					
IN Takaoka, Kunio					
PA Suntory Ltd, Japan					
SO Jpn. Kokai Tokkyo Koho, 19 pp.					
CODEN JKXXAF					
DT Patent					
LA Japanese					
FAN CNT 1					
PATENT NO. KIND DATE APPLICATION NO. DATE					
PI JP 05084081 A2 19930406 JP 1991-203049 19910813 <..					
PRAI JP 1991-203049 19910813					
AB The cDNA for a mouse BMP is cloned from Dunn osteosarcoma cells. The cDNA for BMP was cloned from a library from Dunn mouse osteosarcoma cells by screening with an amino acid sequence-derived probe and by PCR. Expression of the ***BMP*** cDNA in dhfr- ***deficient*** CHO cells using pdKCR-dhfr was shown. The BMP isolated chromatog from the supernatant had bone morphogenetic biol. activity					
L16 ANSWER 73 OF 73 CAPLUS COPYRIGHT 2003 ACS					
AN 1993 161760 CAPLUS					
DN 118 161760					
TI Bone morphogenetic protein 9 (BMP-9) and its pharmaceutical use					
IN Wozney, John M; Celeste, Anthony J					
PA Genetics Institute, Inc., USA					
SO PCT Int Appl., 60 pp					
CODEN PIXXD2					
DT Patent					
LA English					
FAN CNT 4					
PATENT NO. KIND DATE APPLICATION NO. DATE					
PI WO 9300432 A1 19930107 WO 1992-US5374 19920625 <..					
W AU, CA, JP, KR, US					

RW AT BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE
 CA 2108770 AA 19921226 CA 1992-2108770 19920625 <..
 AU 9222699 A1 19930125 AU 1992-22699 19920625 <..
 AU 653472 B2 1994C825
 EP 592562 A1 1994C420 EP 1992-914973 19920625 <..
 EP 592562 B1 1999C107
 R AT BE, CH, DE, DK ES, FR, GB, GR, IT, LI, LU, MC, NL, SE
 JP 06508990 T2 19941013 JP 1992-501662 19920625 <..
 AT 175441 E 19990115 AT 1992-914973 19920625 <..
 ES 2127757 T3 19990501 ES 1992-914973 19920625 <..
 US 5661007 A 19970826 US 1993-50132 19930422 <..
 US 6287816 B1 20010911 US 1994-254353 19940606
 US 6034061 A 20000307 US 1996-750222 19961204 <..
 PRAI US 1991-720590 A 19910625
 WO 1992-US5374 A 19920625
 US 1993-50132 A2 1993C422
 US 1994-254353 A1 19940606
 AB Human BMP-9 and cDNA encoding human BMP-9 are claimed. The cDNAs
 for
 mouse and human BMP-9 were cloned and sequenced. Pharmaceutical
 compns.
 contg. BMP-9 can be used for induction of bone and/or cartilage formation
 and for wound healing and tissue repair (no data).

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FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 11:06 21 ON 13 MAR 2003
 L1 13855 S BONE MORPHOGENETIC PROTEIN? OR BMP
 L2 11378 S BONE MORPHOGENETIC PROTEIN?
 L3 1377 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR
 DISRUPT? OR DEL
 L4 1139 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR
 DISRUPT?)
 L5 871 S L1 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN?)
 L6 501 S L1 AND (KNOCKOUT OR TRANSGEN?)
 L7 258 S L1 (5A) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR
 DISRUPT? OR DE
 L8 137 DUP REM L7 (121 DUPLICATES REMOVED)
 L9 1625 S BMP-4
 L10 174 S L9 AND (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR
 DISRUPT? OR DE
 L11 86 DUP REM L10 (88 DUPLICATES REMOVED)
 L12 203 S L8 OR L11
 L13 28 S L9 (5A) (KNOCKOUT OR TRANSGEN? OR DEFICIEN? OR
 DISRUPT? OR D
 L14 13 DUP REM L13 (15 DUPLICATES REMOVED)
 L15 126 S L8 NOT L14
 L16 73 S L8 AND PY<=2000

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FULL ESTIMATED COST	401 86	402 07

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TOTAL	ENTRY	SESSION
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WEST Search History

DATE: Thursday, March 13, 2003

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L5	L4 same (knockout or knock out or knock-out or transgen\$ or disrupt\$)	18	L5
L4	BMP-4	684	L4
L3	L1 and BMP-4	684	L3
L2	L1 same (knockout or knock out or knock-out or transgen\$ or disrupt\$)	108	L2
L1	bone morphogenetic protein\$ or BMP	4185	L1

END OF SEARCH HISTORY